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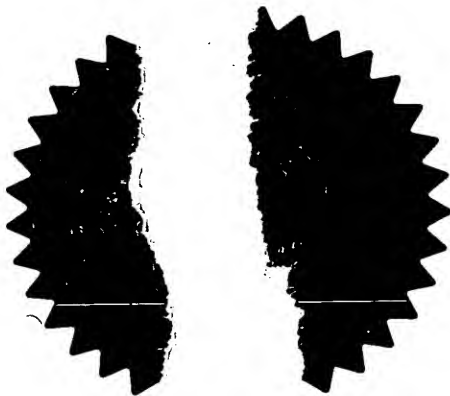


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The Patent Office

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1. Your reference

PA495

2. Patent application number

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0104418.9

3. Full name, address and postcode of the or of each applicant (underline all surnames)

CELTECH CHEMOSCIENCE LIMITED
216 BATH ROAD
SLOUGH
SL1 4EN

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

UK

07904579001

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

CELTECH CHEMOSCIENCE LIMITED
216 BATH ROAD
SLOUGH
SL1 4EN

Patents ADP number (if you know it)

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

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 - b) there is an inventor who is not named as an applicant, or
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Patents Form 1/77

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Description

Claim(s)

Abstract

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11

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Statement of inventorship and right to grant of a patent (Patents Form 7/77)

0

Request for preliminary examination and search (Patents Form 9/77)

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Any other documents (please specify)

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11.

I/We request the grant of a patent on the basis of this application.

FOR AND ON BEHALF OF CRUTECH AEROSPACE LIMITED

Signature

Date

S. J. THORN

22/02/01

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr S THORN

01753 534655

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CHEMICAL COMPOUNDS

5 This invention relates to a series of phenylalanine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T. A., *Nature*, 346, 425, (1990); Springer, T. A., *Cell*, 76, 301, (1994)]. Specific cell surface molecules collectively referred to as cell adhesion molecules mediate many of these interactions.

15 The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 16 different integrin alpha chains and 8 different integrin beta chains have been identified [Newman, P. *et al*, *Molecular Medicine Today*, 304, (1996)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in the field. Thus the integrin $\alpha 4\beta 1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA-4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised to date [Sonnenberg, A., *Current Topics in Microbiology and Immunology*, 184, 7, (1993)].

The importance of integrin function in normal physiological responses is highlighted by two human deficiency diseases in which integrin function is defective. Thus in the disease termed Leukocyte Adhesion Deficiency (LAD) there is a defect in one of the families of integrins expressed on leukocytes [Marlin, S. D. *et al*, *J. Exp. Med.* 164, 855, (1986)]. Patients

suffering from this disease have a reduced ability to recruit leukocytes to inflammatory sites and suffer recurrent infections, which in extreme cases may be fatal. In the case of patients suffering from the disease termed Glanzman's thrombasthenia (a defect in a member of the beta 3 integrin family) there is a defect in blood clotting (Hodivala-Dilke, K. M., J. Clin. Invest. 103, 229, (1999)).

The potential to modify integrin function in such a way as to beneficially modulate cell adhesion has been extensively investigated in animal models using specific antibodies and peptides that block various functions of these molecules [e.g. Issekutz, T. B., J. Immunol. 149, 3394, (1992); Li, Z. *et al*, Am. J. Physiol. 263, L723, (1992); Mitjans, F. *et al*, J. Cell Sci. 108, 2825, (1995); Brooks, P. C. *et al*, J. Clin. Invest. 96, 1815, (1995); Binns, R. M. *et al*, J. Immunol. 157, 4094, (1996); Hammes, H.-P. *et al*, Nature Medicine 2, 529, (1996); Srivata, S. *et al*, Cardiovascular Res. 36, 408 (1997)]. In particular an anti $\alpha_4\beta_7$ -antibody has demonstrated both clinical and histologic improvement of inflammatory activity and disease in a non-human primate model of inflammatory bowel disease [Hesterberg, P.E. *et al*, Gastroenterol, 111, 1373-80 (1996)]. A number of monoclonal antibodies which block integrin function are currently being investigated for their therapeutic potential in human disease, and one, ReoPro, a chimeric antibody against the platelet integrin $\alpha_{IIb}\beta_3$ is in use as a potent anti-thrombotic agent for use in patients with cardiovascular complications following coronary angioplasty.

Integrins recognize both cell surface and extracellular matrix ligands, and ligand specificity is determined by the particular alpha-beta subunit combination of the molecule [Newman, P., *ibid*]. One particular integrin subgroup of interest involves the α_4 chain which can pair with two different beta chains β_1 and β_7 [Sonnenberg, A., *ibid*]. The $\alpha_4\beta_1$ pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes, eosinophils and basophils) although it is absent or only present at low levels on circulating neutrophils. $\alpha_4\beta_1$ binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L., Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least

three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*, Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between $\alpha 4\beta 1$ and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*, J. Clin. Invest. 92, 372, (1993); Abraham, W. M. *et al*, J. Clin. Invest. 93, 776, (1994)].

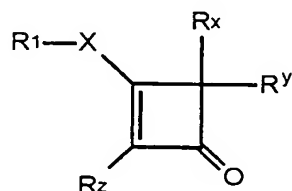
The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B. and Weissman, I. L., EMBO J. 8, 1735, (1989)]. The $\alpha 4\beta 7$ pairing is expressed on certain sub-populations of T and B lymphocytes and on eosinophils [Erle, D. J. *et al*, J. Immunol. 153, 517 (1994)]. Like $\alpha 4\beta 1$, $\alpha 4\beta 7$ binds to VCAM-1 and fibronectin. In addition, $\alpha 4\beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue such as gastrointestinal mucosa termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. MAdCAM-1 is preferentially expressed in the gastrointestinal track. The interaction between $\alpha 4\beta 7$ and MAdCAM-1 may also be important sites of inflammation outside of mucosal tissue [Yang, X.-D. *et al*, PNAS, 91, 12604, (1994)].

Regions of the peptide sequence recognized by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha 4\beta 7$ recognises a LDT sequence in MAdCAM-1 [Birskin, M. J. *et al*, J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al*, J. Biol. Chem., 269, 18668, (1994); Shorff, H. N. *et al*, Biorganic Med. Chem. Lett., 6, 2495, (1996); Vanderslice, P. *et al*, J. Immunol., 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A., *et al*, PNAS, 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is important to be able to identify selective inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of $\alpha 4$ integrins. Members of the group are able to inhibit $\alpha 4$ integrins such as $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. These compounds possess the additional advantage of good pharmacokinetic properties, especially low plasma clearance.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein

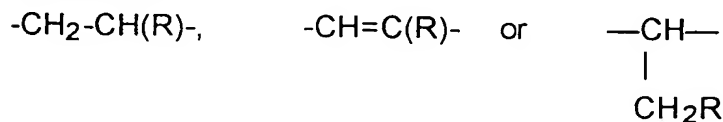
R¹ is a group Ar¹L²Ar²Alk- in which:

Ar¹ is an optionally substituted aromatic or heteroaromatic group;

L² is a covalent bond or a linker atom or group;

Ar² is an optionally substituted arylene or heteroarylene group;

and Alk is a chain



in which R is a carboxylic acid ($-\text{CO}_2\text{H}$) or a derivative or biostere thereof;

X is an -O- or -S- atom or -N(R²)- group in which:

R² is a hydrogen atom or a C₁₋₆alkyl group;

R^x , R^y and R^z which may be the same or different is each an atom or group $-L^1(Alk^1)_n(R^3)_v$ in which L^1 is a covalent bond or a linker atom or group, Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain, R^3 is a hydrogen or halogen atom or group selected from $-OR^{3a}$ [where
 5 R^{3a} is a hydrogen atom or an optionally substituted straight or branched C_{1-6} alkyl group or C_{3-8} cycloalkyl group], $-SR^{3a}$ or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group, n is zero or the integer 1 and v is the integer 1, 2 or 3 provided that when n is zero and L^1 is a covalent
 10 bond v is the integer 1;
 or R^z is an atom or group as previously defined and R^x and R^y are joined together to form an optionally substituted cycloaliphatic or heterocycloaliphatic group;
 and the salts, solvates, hydrates and N-oxides thereof.

15 It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae
 20 hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto ($CH_2C=O$)-enol ($CH=CHOH$) tautomers. Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless
 25 stated otherwise.

30 Optionally substituted aromatic groups represented by Ar^1 when present in the group R^1 include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

35 Optionally substituted heteroaromatic groups represented by the group Ar^1 when present in the group R^1 include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic

fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for
 5 example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include
 10 pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, [2,3-
 15 dihydro]benzothienyl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, e.g. 2,6-naphthyridinyl, or 2,7-naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, iso-
 20 quinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydro-isoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Each aromatic or heteroaromatic group represented by the group Ar¹ may
 25 be optionally substituted on any available carbon or, when present, nitrogen atom. One, two, three or more of the same or different substituents may be present and each substituent may be selected for example from an atom or group -L³(Alk²)_tL⁴(R⁴)_u in which L³ and L⁴, which may be the same or different, is each a covalent bond or a linker
 30 atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk² is an optionally substituted aliphatic or heteroaliphatic chain and R⁴ is a hydrogen or halogen atom or a group selected from optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl, -OR⁵ [where R⁵ is a hydrogen atom, an optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl group], -SR⁵, -NR⁵R⁶
 35 [where R⁶ is as just defined for R⁵ and may be the same or different], -NO₂, -CN, -CO₂R⁵, -SO₃H, -SOR⁵, -SO₂R⁵, -SO₃R⁵, -OCO₂R⁵,

-CONR⁵R⁶, -OCONR⁵R⁶, -CSNR⁵R⁶, -COR⁵, -OCOR⁵, -N(R⁵)COR⁶,
 -N(R⁵)CSR⁶, -SO₂N(R⁵)(R⁶), -N(R⁵)SO₂R⁶, N(R⁵)CON(R⁶)(R⁷) [where R⁷
 is a hydrogen atom, an optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl
 group], -N(R⁵)CSN(R⁶)(R⁷) or -N(R⁵)SO₂N(R⁶)(R⁷), provided that when t
 5 is zero and each of L³ and L⁴ is a covalent bond then u is the integer 1
 and R⁴ is other than a hydrogen atom

When L³ and/or L⁴ is present in these substituents as a linker atom or
 group it may be any divalent linking atom or group. Particular examples
 10 include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-,
 -S(O)₂-, -N(R⁸)- [where R⁸ is a hydrogen atom or an optionally substituted
 straight or branched C₁₋₆alkyl group], -CON(R⁸)-, -OC(O)N(R⁸)-,
 -CSN(R⁸)-, -N(R⁸)CO-, -N(R⁸)C(O)O-, -N(R⁸)CS-, -S(O)₂N(R⁸)-,
 -N(R⁸)S(O)₂-, -N(R⁸)O-, -ON(R⁸)-, -N(R⁸)N(R⁸)-, -N(R⁸)CON(R⁸)-,
 15 -N(R⁸)CSN(R⁸)-, or -N(R⁸)SO₂N(R⁸)- groups. Where the linker group
 contains two R⁸ substituents, these may be the same or different.

When R^{3a}, R⁴, R⁵, R⁶, R⁷ and/or R⁸ is present as a C₁₋₆alkyl group it may
 be a straight or branched C₁₋₆alkyl group, e.g. a C₁₋₃alkyl group such as a
 20 methyl or ethyl group. C₃₋₈cycloalkyl groups represented by R^{3a}, R⁴, R⁵,
 R⁶ and/or R⁷ include C₃₋₆cycloalkyl groups e.g. cyclopropyl, cyclobutyl,
 cyclopentyl and cyclohexyl groups. Optional substituents which may be
 present on such groups include for example one, two or three substituents
 which may be the same or different selected from halogen atoms, for
 25 example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C₁₋₆
 alkoxy e.g. methoxy or ethoxy groups.

When the groups R⁵ and R⁶ or R⁶ and R⁷ are both C₁₋₆alkyl groups these
 groups may be joined, together with the N atom to which they are
 30 attached, to form a heterocyclic ring. Such heterocyclic rings may be
 optionally interrupted by a further heteroatom selected from -O-, -S- or
 -N(R⁵)-. Particular examples of such heterocyclic rings include piperidinyl,
 morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl
 rings.

When Alk² is present as an optionally substituted aliphatic or heteroaliphatic chain it may be any optionally substituted aliphatic or heteroaliphatic chain as described hereinafter for Alk¹.

- 5 Halogen atoms represented by R⁴ in the optional Ar¹ substituents include fluorine, chlorine, bromine, or iodine atoms.

10 Examples of the substituents represented by -L³(Alk¹)_tL⁴(R⁴)_u when present in Ar¹ groups in compounds of the invention include atoms or groups -L³Alk²L⁴R⁴, -L³Alk²R⁴, -L³R⁴, -R⁴ and -Alk²R⁴ wherein L³, Alk², L⁴ and R⁴ are as defined above. Particular examples of such substituents include -L³CH₂L⁴R⁴, -L³CH(CH₃)L⁴R⁴, -L³CH(CH₂)₂L⁴R⁴, -L³CH₂R⁴, -L³CH(CH₃)R⁴, -L³(CH₂)₂R⁴, -CH₂R⁴, -CH(CH₃)R⁴, -(CH₂)₂R⁴ and -R⁴ groups.

15 Thus Ar¹ in compounds of the invention may be optionally substituted for example by one, two, three or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, and/or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C₃₋₈cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or -C(OH)(CF₃)₂, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxy-propylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, haloC₁₋₆alkyl, e.g. -CF₃, -CHF₂, CH₂F, haloC₁₋₆alkoxy, e.g. -OCF₃, -OCHF₂, -OCH₂F, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂R⁵ e.g. -CO₂CH₃ or -CO₂C(CH₃)₃, C₁₋₆alkanoyl e.g. acetyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), -SO₃Alk³, C₁₋₆alkylsulphinyl, e.g. methylsulphinyl, C₁₋₆alkylsulphonyl, e.g.

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- methylsulphonyl, aminosulphonyl ($-\text{SO}_2\text{NH}_2$), C_{1-6} alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6} dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-\text{CONH}_2$), C_{1-6} alkyl-aminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6} dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, amino C_{1-6} alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6} dialkylamino C_{1-6} alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6} dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6} alkylaminocarbonyl C_{1-6} alkylamino, e.g. methylaminocarbonylmethyl-amino, aminothiocarbonylamino, C_{1-6} alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6} dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6} alkylaminothiocarbonyl C_{1-6} alkylamino, e.g. ethylaminothiocarbonylmethylamino, C_{1-6} alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6} dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino ($-\text{NHSO}_2\text{NH}_2$), C_{1-6} alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonyl-amino, C_{1-6} dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6} alkanoylamino, e.g. acetylamino, amino C_{1-6} alkanoylamino e.g. aminoacetylamino, C_{1-6} dialkylamino C_{1-6} alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6} alkanoylamino C_{1-6} alkyl, e.g. acetylaminomethyl, C_{1-6} alkanoylamino C_{1-6} alkylamino, e.g. acetamidoethylamino, C_{1-6} alkoxy-carbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.
- L^2 when present as part of the group R^1 in compounds of the invention may be a linker atom or group L^{2a} or a linker $-(\text{Alk}^3)\text{L}^{2a}$, where Alk^3 is an optionally substituted aliphatic or heteroaliphatic chain which may be any such chain as described hereinafter for Alk^1 , and L^{2a} may be any linker atom or group as described hereinbefore for L^3 .

Optionally substituted arylene groups represented by Ar^2 when present as part of the group R^1 include those aromatic groups as previously described for Ar^1 .

- 5 Optionally substituted heteroarylene groups represented by Ar^2 when present as part of the group R^1 include those heteroaromatic groups as previously described for Ar^1 .

10 Each divalent arylene or heteroarylene group represented by Ar^2 may be attached to the remainder of the molecule through any available ring carbon or nitrogen atoms.

15 The arylene and heteroarylene groups represented by Ar^2 may be optionally substituted by one, two or more substituents selected from the atoms or groups $-L^3(Alk^2)_tL^4(R^4)_u$ described herein. Where two of these atoms or groups are present they may be the same or different.

20 When the group R is present in R^1 in compounds of the invention as a derivative of a carboxylic acid it may be for example a carboxylic acid ester or amide. Particular esters and amides include $-CO_2Alk^7$ and $-CONR^5R^6$ groups as defined herein. When R is a biostere of a carboxylic acid it may be for example a tetrazole or other acid such as phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an acylsulphonamide group.

25 Esters ($-CO_2Alk^7$) and amide ($-CONR^5R^6$) derivatives of the carboxylic acid group ($-CO_2H$) in compounds of formula (1) may advantageously be used as prodrugs of the active compound. Such prodrugs are compounds which undergo biotransformation to the corresponding carboxylic acid prior to exhibiting their pharmacological effects and the invention particularly extends to produgs of the acids of formula (1). Such prodrugs are well known in the art, see for example International Patent Application No. WO00/23419, Bodor, N. (Alfred Benzon Symposium, 1982, 17, 156-177), Singh, G. et al (J. Sci. Ind. Res., 1996, 55, 497-510) and Bundgaard, H.,
30 (Design of Prodrugs, 1985, Elsevier, Amsterdam).
35

Esterified carboxyl groups represented by the group $-\text{CO}_2\text{Alk}^7$ include groups wherein Alk^7 is a straight or branched optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; an optionally substituted C_{2-8} alkenyl group such as a propenyl e.g. 2-propenyl or butenyl e.g. 2-butenyl or 3-butenyl group, an optionally substituted C_{2-8} alkynyl group such as a ethynyl, propynyl e.g. 2-propynyl or butynyl e.g. 2-butynyl or 3-butynyl group, an optionally substituted C_{3-8} cycloalkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C_{3-8} cycloalkyl C_{1-8} alkyl group such as a cyclopentylmethyl, cyclohexylmethyl or cyclohexylethyl group; an optionally substituted C_{3-8} heterocycloalkyl C_{1-6} alkyl group such as a morpholinyl-N-ethyl, thiomorpholinyl-N-methyl, pyrrolidinyl-N-ethyl, pyrrolidinyl-N-propyl, piperidinyl-N-ethyl, pyrazolidinyl-N-methyl or piperazinyl-N-ethyl group; an optionally substituted C_{1-6} alkyloxy C_{1-6} alkyl group such as a methyloxyethyl or propyloxyethyl group; an optionally substituted C_{1-6} alkylthio C_{1-6} alkyl group such as an ethylthioethyl group; an optionally substituted C_{1-6} alkylsulfinyl C_{1-6} alkyl group such as an methylsulfinylethyl group; an optionally substituted C_{1-6} alkylsulfonyl C_{1-6} alkyl group such as an methylsulfonylmethyl group; an optionally substituted C_{3-8} cycloalkyloxy C_{1-6} alkyl group such as a cyclohexyloxymethyl group; an optionally substituted C_{3-8} cycloalkylthio C_{1-6} alkyl group such as a cyclopentylthiomethyl group; an optionally substituted C_{3-8} cycloalkylsulfinyl C_{1-6} alkyl group such as a cyclopentylsulfinylmethyl group; an optionally substituted C_{3-8} cycloalkylsulfonyl C_{1-6} alkyl group such as a cyclopentylsulfonylmethyl group; an optionally substituted C_{1-6} alkyloxycarbonyl C_{1-6} alkyl group such as isobutoxycarbonylpropyl group; an optionally substituted C_{1-6} alkyloxycarbonyl C_{1-6} alkenyl group such as isobutoxycarbonylpentenyl group; an optionally substituted C_{1-6} alkyloxycarbonyloxy C_{1-6} alkyl group such as an isopropoxycarbonyloxyethyl e.g. a 1-(isopropoxycarbonyloxy)ethyl, 2-(isopropoxycarbonyloxy)ethyl or ethyloxycarbonyloxymethyl group; an optionally substituted C_{1-6} alkyloxycarbonyloxy C_{1-6} alkenyl group such as a isopropoxycarbonyloxybutenyl group, an optionally substituted C_{3-8} cycloalkyloxycarbonyloxy C_{1-6} alkyl group such as a cyclohexyloxycarbonyloxyethyl, e.g. a 2-(cyclohexyloxycarbonyloxy)ethyl group, an optionally substituted N-di- C_{1-8} alkylamino C_{1-8} alkyl group such as a N-

dimethylaminoethyl or N-diethylaminoethyl group; an optionally substituted N-C₆₋₁₂aryl-N-C₁₋₆alkylaminoC₁₋₆alkyl group such as a N-phenyl-N-methylaminomethyl group; an optionally substituted N-di-C₁₋₈alkyl-carbamoylC₁₋₈alkyl group such as a N-diethylcarbamoylmethyl group; an
 5 optionally substituted C₆₋₁₀arylC₁₋₆alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C₆₋₁₀aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₀aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl,
 10 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; a C₆₋₁₂arylthioC₁₋₈alkyl group such as an optionally substituted phenylthioethyl group; a C₆₋₁₂arylsulfinylC₁₋₈alkyl group such as an optionally substituted phenylsulfinylmethyl group; a C₆₋₁₂arylsulfonylC₁₋₈alkyl group such as an optionally substituted phenylsulfonylmethyl group; an optionally substituted
 15 C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a acetoxymethyl, ethoxycarbonyloxyethyl, pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; an optionally substituted C₄₋₈imidoC₁₋₈alkyl group such as a succinimidomethyl or phthalamidoethyl group; a C₆₋₁₂aroyloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxyethyl or
 20 benzoyloxypropyl group or a triglyceride such as a 2-substituted triglyceride e.g. a 1,3-di-C₁₋₈alkylglycerol-2-yl group such as a 1,3-diheptylglycerol-2-yl group. Optional substituents present on the Alk⁷ group include R^{13a} substituents described below.

25 It will be appreciated that in the forgoing list of Alk⁷ groups the point of attachment to the remainder of the compound of formula (1) is via the last described part of the Alk⁷ group. Thus, for example a methoxyethyl group would be attached by the ethyl group, whilst a morpholinyl-N-ethyl group would be attached via the N-ethyl group.

30

It will be further appreciated that in the forgoing list of Alk⁷ groups, where not specifically mentioned, alkyl groups may be replaced by alkenyl or alkynyl groups where such groups are as previously defined for Alk¹. Additionally these alkyl, alkenyl or alkynyl groups may optionally be
 35 interrupted by one, two or three linker atoms or groups where such linker atoms and groups are as previously defined for L³.

When the groups R^2 is present in compounds of the invention as a C_{1-6} alkyl group it may be for example a straight or branched C_{1-6} alkyl group e.g. a C_{1-3} alkyl group such as a methyl or ethyl group.

5

When present in the group R^X , R^Y and/or R^Z in compounds of formula (1) the linker atom or group represented by L^1 may be any linker atom or group as described above for the linker atom or group L^3 .

- 10 When Alk^1 is present in the group R^X , R^Y and/or R^Z in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene chains.

15

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-CH_2-$, $-(CH_2)_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$,
 20 $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-(CH_2)_2CCH-$ groups.

- Heteroaliphatic chains represented by Alk^1 when present in the group R^X ,
 25 R^Y and/or R^Z in compounds of formula (1) include the aliphatic chains just described for Alk^1 but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^5 where L^5 is as defined above for L^3 when L^3 is a linker atom or group. Each L^5 atom or group may
 30 interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group. Particular examples include optionally substituted $-CH_2L^5-$, $-L^5CH_2CH_2-$, $-CH_2L^5CH_2CH_2-$, $-(CH_2)_2L^5CH_2-$, $-(CH_2)_3L^5CH_2-$, $-L^5(CH_2)_3-$, $-CH_2L^5CH_2CHL^5CH_2-$ and $-(CH_2)_2L^5CH_2CH_2-$ chains

35

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, -CO₂H, -CO₂R⁹, where R⁹ is an optionally substituted straight or branched C₁₋₆alkyl group as defined above for R⁴, -CONHR⁹, -CON(R⁹)₂, -COCH₃, C₁₋₆alkoxy, e.g. methoxy or ethoxy, thiol, -S(O)R⁹, -S(O)₂R⁹, C₁₋₆alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include -NHR⁹ and -N(R⁹)₂ groups. Where two R⁹ groups are present in any of the above substituents these may be the same or different.

Optionally substituted cycloaliphatic groups represented by the group R³ when present in the group R^x, R^y and/or R^z in compounds of the invention include optionally substituted C₃₋₁₀ cycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀ cycloalkyl, e.g. C₃₋₇ cycloalkyl or C₃₋₁₀ cycloalkenyl, e.g. C₃₋₇ cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by the group R³ when present in the group R^x, R^y and/or R^z include optionally substituted C₃₋₁₀ heterocycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀ heterocycloalkyl, e.g. C₃₋₇ heterocycloalkyl, or C₃₋₁₀ heterocycloalkenyl, e.g. C₃₋₇ heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L⁵ as defined above.

Optionally substituted polycycloaliphatic groups represented by the group R³ when present in the group R^x, R^y and/or R^z include optionally substituted C₇₋₁₀ bi- or tricycloalkyl or C₇₋₁₀ bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group R³ include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L⁵ atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group R³

include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranal, e.g. 2- or 4-pyranal, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups represented by the group R^3 include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6} alkyl, e.g. methyl, ethyl or propyl, halo C_{1-6} alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6} alkoxy, e.g. methoxy, ethoxy or propoxy, halo C_{1-6} alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6} alkylthio e.g. methylthio, ethylthio or propylthio, or $-(Alk^4)_gR^{10}$ groups in which Alk^4 is a straight or branched C_{1-3} alkylene chain, g is zero or an integer 1 and R^{10} is a -OH, -SH, $-N(R^{11})_2$, (in which R^{11} is an atom or group as defined herein for R^7) $-CN$, $-CO_2R^{11}$, $-NO_2$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-COR^{11}$, $-CSN(R^{11})_2$, $-N(R^{11})COR^{11}$, $-N(R^{11})CSR^{11}$, $-SO_2N(R^{11})_2$, $-N(R^{11})SO_2R^{11}$, $-N(R^{11})CON(R^{11})_2$, $-N(R^{11})CSN(R^{11})$, $N(R^{11})SO_2N(R^{11})_2$ or optionally substituted phenyl group. Where two R^{11} atoms or groups are present in these substituents these may be the same or different or joined to form a heterocyclic ring as previously described when R^5 and R^6 are joined together. Optionally substituted phenyl groups include phenyl substituted by one, two or three of the R^{13} groups described below

Additionally, when the group R^3 is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^6)_p(Alk^5)_qR^{12}$ in which L^6 is $-C(O)-$, $-C(O)O-$,

-C(S)-, -S(O)₂-, -CON(R⁸)-, -CSN(R⁸)- or SO₂N(R⁸)-; p is zero or an integer 1; Alk⁵ is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R¹² is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

C₁₋₃alkylene chains represented by Alk⁴ include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH(CH₃)CH₂- and -CH₂CH(CH₃)- chains.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk⁵ include those optionally substituted chains described above for Alk¹. Optional substituents which may be present on these groups include those described above in relation to Alk¹.

Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocycloaliphatic groups represented by R¹² include those groups just described for the group R³. Optional substituents which may be present on those groups include those described above in relation to R³ cycloaliphatic groups.

Aromatic or heteroaromatic groups represented by R¹² include those groups described herein for the group Ar¹. Optional substituents which may be present on these groups include those R¹³ optional substituents described hereinafter.

When the group R³ is an optionally substituted aromatic or heteroaromatic group it may be for example an aromatic or heteroaromatic group as described herein for the group Ar¹.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group R³ include one, two, three or more substituents, each selected from an atom or group R¹³ in which R¹³ is -R^{13a} or -Alk⁶(R^{13a})_m, where R^{13a} is a halogen atom, or an amino (-NH₂), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), substituted thiol, -COR¹⁴ [where R¹⁴ is an -Alk⁶(R^{13a})_m, aryl or

heteroaryl group], -CSR¹⁴, -SO₃H, -SOR¹⁴, -SO₂R¹⁴, -SO₃R¹⁴, -SO₂NH₂,
 -SO₂NHR¹⁴, -SO₂N(R¹⁴)₂, -CONH₂, -CSNH₂, -CONHR¹⁴, -CSNHR¹⁴,
 -CON[R¹⁴]₂, -CSN(R¹⁴)₂, -N(R¹¹)SO₂R¹⁴, -N(SO₂R¹⁴)₂,
 -NH(R¹¹)SO₂NH₂, -N(R¹¹)SO₂NHR¹⁴, -N(R¹¹)SO₂N(R¹⁴)₂,
 5 -N(R¹¹)COR¹⁴, -N(R¹¹)CONH₂, -N(R¹¹)CONHR¹⁴, -N(R¹¹)CON(R¹⁴)₂,
 -N(R¹¹)CSNH₂, -N(R¹¹)CSNHR¹⁴, -N(R¹¹)CSN(R¹⁴)₂, -N(R¹¹)CSR¹⁴,
 -N(R¹¹)C(O)OR¹⁴, -SO₂NHet¹ [where -NHet¹ is an optionally substituted
 C₅₋₇cyclicamino group optionally containing one or more other -O- or -S-
 atoms or -N(R¹¹)-, -C(O)-, -C(S)-, S(O) or -S(O)₂ groups], -CONHet¹,
 10 -CSNHet¹, -N(R¹¹)SO₂NHet¹, -N(R¹¹)CONHet¹, -N(R¹¹)CSNHet¹,
 -SO₂N(R¹¹)Het² [where Het² is an optionally substituted monocyclic C₅₋₇
 carbocyclic group optionally containing one or more -O- or -S- atoms or
 -N(R¹¹)-, -C(O)- or -C(S)- groups], -Het², -CON(R¹¹)Het², -CSN(R¹¹)Het²,
 -N(R¹¹)CON(R¹¹)Het², -N(R¹¹)CSN(R¹¹)Het², aryl or heteroaryl group;
 15 Alk⁶ is a straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆
 alkynylene chain, optionally interrupted by one, two or three -O- or -S-
 atoms or -S(O)_n [where n is an integer 1 or 2] or -N(R¹⁵)- groups [where
 R¹⁵ is a hydrogen atom or C₁₋₆alkyl, e.g. methyl or ethyl group]; and m is
 zero or an integer 1, 2 or 3. It will be appreciated that when two R¹¹ or R¹⁴
 20 groups are present in one of the above substituents, the R¹¹ or R¹⁴ groups
 may be the same or different.

When in the group -Alk⁶(R^{13a})_m m is an integer 1, 2 or 3, it is to be
 understood that the substituent or substituents R^{13a} may be present on
 25 any suitable carbon atom in -Alk⁶. Where more than one R^{13a} substituent
 is present these may be the same or different and may be present on the
 same or different atom in -Alk⁶. Clearly, when m is zero and no
 substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain
 represented by Alk⁶ becomes an alkyl, alkenyl or alkynyl group.

30 When R^{13a} is a substituted amino group it may be for example a group
 -NHR¹⁴ [where R¹⁴ is as defined above] or a group -N(R¹⁴)₂ wherein each
 R¹⁴ group is the same or different.

35 When R^{13a} is a halogen atom it may be for example a fluorine, chlorine,
 bromine, or iodine atom.

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{14}$ or a $-SR^{14}$ or $-SC(=NH)NH_2$ group respectively.

- 5 Esterified carboxyl groups represented by the group R^{13a} include groups of formula $-CO_2Alk^8$ wherein Alk^8 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a $C_{6-12}arylC_{1-8}alkyl$ group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a $C_{6-12}aryl$ group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a $C_{6-12}aryloxyC_{1-8}alkyl$ group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted $C_{1-8}alkanoyloxyC_{1-8}alkyl$ group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a $C_{6-12}aroyloxyC_{1-8}alkyl$ group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^8 group include R^{13a} substituents described above.
- 10
- 15
- 20 When Alk^6 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three $-O-$ or $-S-$, atoms or $-S(O)-$, $-S(O)_2-$ or $-N(R^8)-$ groups.
- 25

- Aryl or heteroaryl groups represented by the groups R^{13a} or R^{14} include mono- or bicyclic optionally substituted $C_{6-12}aromatic$ or $C_{1-9}heteroaromatic$ groups as described above for the group Ar^1 . The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.
- 30

- When $-NHet^1$ or $-Het^2$ forms part of a substituent R^{13} each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or
- 35

cyclohexyl group. Optional substituents which may be present on -NHet¹ or -Het² include those optional substituents described above in relation to aliphatic chains represented by Alk¹.

- 5 Particularly useful atoms or groups represented by R¹³ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, e.g. t-butyloxycarbonylpiperazinyl, pyrrolidinyl, dioxolanyl, dioxanyl,
- 10 oxazolidinyl, thiazolidinyl, imidazolidinyl or piperidinyl, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy,
- 15 optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₄₋₇cycloalkyl, e.g. cyclobutyl, cyclopentyl, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino, ethylamino or propylamino, C₆₋₁₂arylC₁₋₆alkylamino, e.g. benzylamino, 4-fluorobenzyl-
- 20 amino or 4-hydroxyphenylethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, aminoC₁₋₆alkylamino, e.g. aminoethylamino or amino-propylamino, optionally substituted Het¹NC₁₋₆alkylamino, e.g. 3-morpho-
- 25 linopropylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC₁₋₆alkylamino, e.g. 2-hydroxyethylamino, 3-hydroxypropylamino or 3-hydroxybutylamino,
- 30 imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁷ [where Alk⁷ is as defined above], C₁₋₆alkanoyl e.g. acetyl, propyryl or butyryl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), -SO₃Alk⁷,
- 35 C₁₋₆alkylsulphinyl, e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl or propyl-

sulphonyl, aminosulphonyl ($-\text{SO}_2\text{NH}_2$), C_{1-6} alkylaminosulphonyl, e.g. methylaminosulphonyl, ethylaminosulphonyl or propylaminosulphonyl C_{1-6} dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-\text{CONH}_2$), C_{1-6} alkylaminocarbonyl, e.g. methylaminocarbonyl, ethylaminocarbonyl or propylaminocarbonyl, C_{1-6} dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, amino C_{1-6} alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6} alkylamino C_{1-6} alkylaminocarbonyl, e.g. methylaminoethylaminocarbonyl, C_{1-6} dialkylamino C_{1-6} alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6} dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6} alkylaminocarbonyl C_{1-6} alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonylamino, C_{1-6} alkylaminothiocabonylamino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C_{1-6} dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonylamino, C_{1-6} alkylaminothiocabonyl C_{1-6} alkylamino, e.g. ethylaminothiocabonylmethylamino, $-\text{CONHC}(=\text{NH})\text{NH}_2$, C_{1-6} alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, halo C_{1-6} alkylsulphonylamino, e.g. trifluoromethylsulphonylamino, C_{1-6} dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino ($-\text{NHSO}_2\text{NH}_2$), C_{1-6} alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6} dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonyl C_{1-6} alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6} alkanoylamino, e.g. acetylamino, amino C_{1-6} alkanoylamino e.g. aminoacetylamino, C_{1-6} dialkylamino C_{1-6} alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6} alkanoylamino C_{1-6} alkyl, e.g. acetylamino-methyl, C_{1-6} alkanoylamino C_{1-6} alkylamino, e.g. acetamidoethylamino, C_{1-6} alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylamino C_{1-6} alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{13} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6} alkylenedioxy group such as methylenedioxy or ethylenedioxy.

5

It will be appreciated that where two or more R^{13} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R^3 .

10

When the groups R^x and R^y are joined together to form an optionally substituted spiro linked cycloaliphatic or heterocycloaliphatic group joined to the cyclobutenone ring as defined by formula (1) it may be any such cycloaliphatic or heterocycloaliphatic group as previously described for R^3 .

15

Optional substituents which may be present on such spiro linked cycloaliphatic or heteroaliphatic groups include those optional substituents as described in relation to R^3 .

20

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

25

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

30

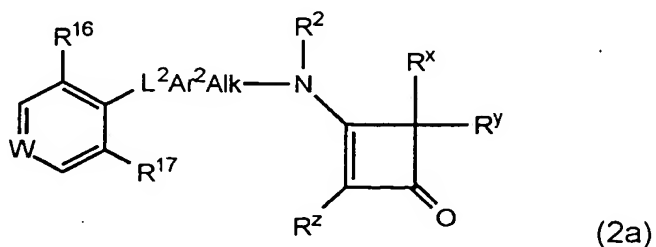
Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

35

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

- 5 In the compounds according to the invention the group R^1 is preferably an $Ar^1L^2Ar^2Alk$ - group. In compounds of this type Ar^1 is preferably an optionally substituted phenyl, monocyclic heteroaromatic or bicyclic heteroaromatic group. Particularly useful monocyclic heteroaromatic groups are optionally substituted five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. Particularly useful substituents present on these Ar^1 groups include halogen atoms or
- 10 alkyl, haloalkyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-CO_2H$, $-CO_2CH_3$, $-NO_2$, $-N(R^5)COR^6$ or $-CN$ groups as described above in relation to the compounds of formula (1). Particularly useful bicyclic heteroaromatic groups represented by Ar^1 include optionally substituted ten-membered fused-ring heteroaromatic groups containing one or two heteroatoms, especially nitrogen atoms. Particular examples include optionally substituted naphthyridinyl, especially 2,6-naphthyridinyl, 2,7-naphthyridinyl, quinolinyl and isoquinolinyl, especially isoquinolin-1-yl groups. Particular optional substituents include those just described for monocyclic heteroaromatic groups. Additionally, in the compounds according to the
- 20 invention X is preferably an $-N(R^2)$ - group.

A particularly useful group of compounds according to the invention has the formula (2a):



wherein -W= is -CH= or -N=;

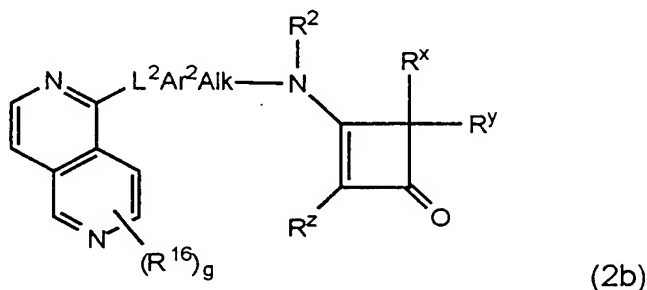
R¹⁶ and R¹⁷, which may be the same or different is each a hydrogen atom or an atom or group -L³(Alk²)_tL⁴(R⁴)_u in which L³, Alk², t, L⁴ R⁴ and u are as defined previously;

- 5 L², Ar², Alk, R², R^x, R^y and R^z are as defined for formula (1);
and the salts, solvates, hydrates and N-oxides thereof.

-W= in compounds of formula (2a) is preferably -N=.

- 10 R¹⁶ and R¹⁷ in compounds of formula (2a) is each preferably as particularly described above for compounds of formula (1), other than a hydrogen atom. Particularly useful R¹⁶ and R¹⁷ substituents include halogen atoms, especially fluorine or chlorine atoms, or methyl, halomethyl, especially -CF₃, -CHF₂ or -CH₂F, methoxy or halomethoxy,
15 especially -OCF₃, -OCHF₂ or -OCH₂F groups.

A further particularly useful group of compounds according to the invention has the formula (2b):



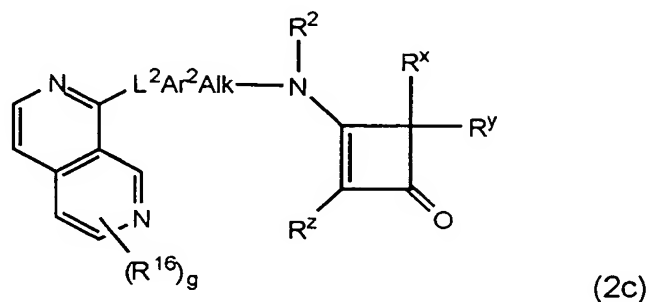
wherein g is the integer 1,2,3 or 4;

R¹⁶, L², Ar², Alk, R², R^x, R^y and R^z are as defined for formula (2a);
and the salts, solvates, hydrates and N-oxides thereof.

- 25 Each R¹⁶ atom or group in compounds of formula (2b) may be independently selected from an atom or group -L³(Alk²)_tL⁴(R⁴)_u in which L², Alk², t, L³, R⁴ and u are as previously defined. Particularly useful R¹⁶ substituents when present in compounds of formula (2b) include halogen
30 atoms, especially fluorine, chlorine or bromine atoms, or methyl, halomethyl, especially -CF₃, methoxy or halomethoxy, especially -OCF₃,

-CN, -CO₂Me, -NO₂, amino (-NH₂), substituted amino (-NR⁵R⁶) and -N(R⁵)COCH₃, especially -NHCOCH₃ groups and optionally substituted phenyl, furyl, thienyl, imidazolyl, pyridyl and pyrimidinyl groups.

- 5 A further particularly useful group of compounds according to the invention has the formula (2c):

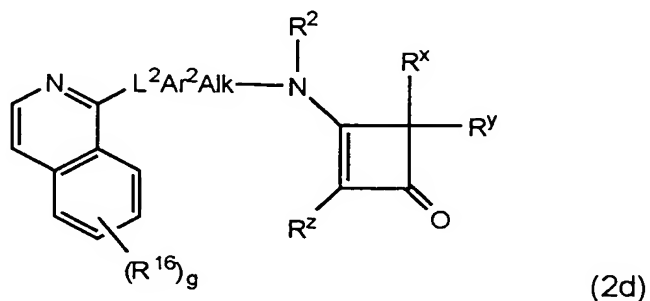


- 10 wherein R¹⁶, g, L², Ar², Alk, R², R^x, R^y and R^z are as defined for formula (2b);
and the salts, solvates, hydrates and N-oxides thereof.

- 15 Each R¹⁶ atom or group in compounds of formula (2c) may be independently selected from an atom or group -L³(Alk²)_nL⁴(R⁴)_u as previously defined for compounds of formula (2b).

A further particularly useful group of compounds according to the invention has the formula (2d):

20



wherein R¹⁶, g, L², Ar², Alk, R², R^x, R^y and R^z are as defined for formula (2b):

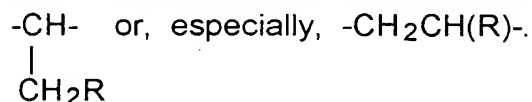
and the salts, solvates, hydrates and N-oxides thereof.

Each R^{16} atom or group in compounds of formula (2d) may be independently selected from an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ as previously defined for compounds of formula (2b).

In one preferred class of compounds of formula (2d) at least one R^{16} atom or group is present at the 3-position of the isoquinoline ring. In a preferred group of compounds of this class R^{16} is an optionally substituted phenyl ring.

It will be understood that compounds according to formulae (2a), (2b), (2c) and (2d) include, where applicable, the corresponding hydroxy tautomers.

Alk in compounds of the invention is preferably:



In one preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R is a $-CO_2H$ group.

In another preferred class of compounds of formulae (1) and (2) R is an esterified carboxyl group of formula $-CO_2Alk^7$. In this class of compound Alk^7 is preferably a C_{1-8} alkyl group, especially a methyl, ethyl, propyl or isopropyl group, an optionally substituted C_{6-10} aryl group, especially a phenyl group, an optionally substituted C_{6-10} aryl C_{1-6} alkyl group, especially a benzyl group, a C_{3-8} heterocycloalkyl C_{1-6} alkyl group, especially a morpholinyl-N-ethyl group or a C_{1-6} alkyloxy C_{1-6} alkyl group, especially a methoxyethyl group. Especially preferred esterified carboxyl groups include $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$ and $-CO_2CH(CH_3)_2$ groups.

In general in compounds of formulae (1), (2a), (2b), (2c) and (2d) R^2 is preferably a hydrogen atom.

In compounds of formula (2a) L^2 is preferably L^{2a} where L^{2a} is a $-\text{CON}(\text{R}^8)-$ group, especially a $-\text{CONH}-$ group or a $-(\text{Alk}^3)\text{L}^{2a}-$ group, especially a $-\text{CH}_2\text{O}-$ group.

- 5 In general in compounds of formulae (2b), (2c) and (2d) L^2 is preferably L^{2a} where L^{2a} is an $-\text{O}-$ atom or $-\text{N}(\text{R}^8)-$ group. An especially useful $-\text{N}(\text{R}^8)-$ group is $-\text{NH}-$.

- 10 The group Ar^2 in compounds of formulae (1), (2a) and (2b) is preferably an optionally substituted phenylene group. Particularly useful groups include optionally substituted 1,4-phenylene groups.

- 15 In one generally preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x , R^y and/or R^z is an optionally substituted alkyl group, most preferably an optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, n-heptyl, or n-hexyl group. Particularly preferred optional substituents which may be present on such R^x , R^y and/or R^z alkyl groups include halogen atoms, especially fluorine or chlorine atoms, alkoxy groups, especially methoxy, haloalkoxy groups, especially $-\text{OCF}_3$, $-\text{CN}$, $-\text{CO}_2\text{Me}$, $-\text{NO}_2$, substituted amino ($-\text{NR}^5\text{R}^6$) especially $-\text{NHCH}_3$ and $-\text{N}(\text{CH}_3)_2$ and optionally substituted phenyl groups.
- 20

- 25 In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^z is a hydrogen atom.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x is a hydrogen atom.

- 30 In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^z is each a hydrogen atom.

- 35 In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x is a hydrogen atom and R^y is an optionally substituted alkyl group as just described.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^z is each a hydrogen atom and R^y is an optionally substituted alkyl group as just described.

- 5 In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x is a hydrogen atom and R^y and R^z is each an optionally substituted alkyl group as just described.

- 10 In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^y is each an optionally substituted alkyl group as just described.

- 15 In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^y is each an optionally substituted alkyl group as just described and R^z is a hydrogen atom.

- 20 In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x , R^y and R^z is each an optionally substituted alkyl group as just described.

- 25 In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^x and R^y are joined to form an optionally substituted spiro linked cycloaliphatic group, particularly an optionally substituted cyclopentyl or cyclohexyl group. Particularly preferred optional substituents which may be present on such spiro linked cycloaliphatic groups include halogen atoms, especially fluorine or chlorine atoms, alkoxy groups, especially methoxy, haloalkoxy groups, especially $-OCF_3$, $-CN$, $-CO_2Me$, $-NO_2$ and substituted amino ($-N(R^{11})_2$), especially $-NCH_3$ and $-N(CH_3)_2$ groups.

- 30 Compounds according to the invention are potent and selective inhibitors of α_4 integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

- 35 The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders

including inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders,

5

Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

10

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

15

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

20

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

30

35

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

- 5 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations
10 for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively,
15 the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting
20 formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the
25 form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

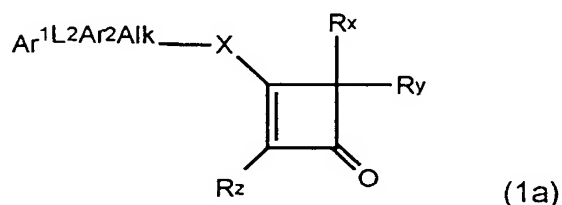
30 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

35 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound

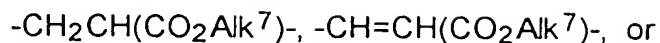
chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar^1 , Ar^2 , Alk, R^1 , R^2 , R^3 , L^1 , L^2 , Alk¹, R^x , R^y , R^z and n when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

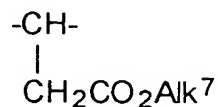
Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (1a):



where Alk represents a group



5

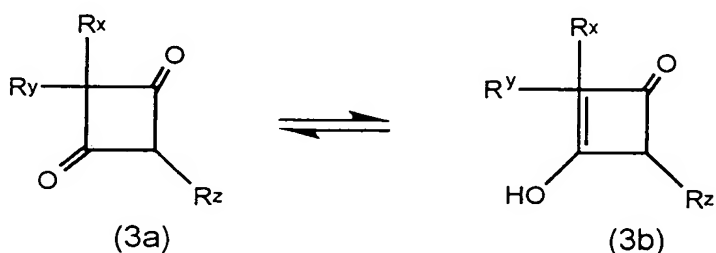


10 [where Alk⁷ is an alkyl group for example a C₁₋₆alkyl group]

The hydrolysis may be performed using either an acid or a base depending on the nature of Alk⁷, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium, sodium or
 15 potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at a temperature from ambient to the reflux temperature. Where desired, mixtures of such solvents may be used.

20

According to a further aspect of the invention a compound of formula (1) may be prepared by condensation of a compound of formula (3):



25

where compounds of formula (3) exist as two tautomeric isomers, (3a) and (3b) in solution with an amine of formula R¹R²NH, an alcohol of formula R¹OH or a thiol of formula R¹SH.

30

The reaction may be performed in an inert solvent or mixture of solvents, for example a hydrocarbon such as an aromatic hydrocarbon e.g. benzene or toluene and/or a halogenated hydrocarbon such as 1,2-dichloroethane,

or dichloromethane at a temperature from 0°C to the reflux temperature. Where necessary, for example when a salt of an amine R^1R^2NH is used, an organic base such as diisopropylethylamine can be added.

- 5 Any carboxylic acid group present in the intermediate of formula (3) or the amine R^1R^2NH , alcohol R^1OH or thiol R^1SH may need to be protected during the displacement reaction, for example as an ethyl ester. The desired acid may then be obtained through subsequent hydrolysis, for example as particularly described above and generally described below.

10

The displacement reaction may also be carried out on an intermediate of formula 4 (see below) under the conditions just described..

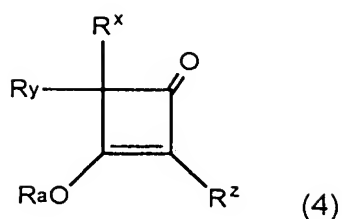
- 15 Where desired the displacement reaction may also be performed on an intermediate of formulae (3), R^1R^2NH , R^1OH or R^1SH which is linked, for example via its R , R^1 or R^3 group, to a solid support, such as a polystyrene resin. After the reaction the desired compound of formula (1) may be displaced from the support by any convenient method, depending on the original linkage chosen.

20

- Intermediates of formulae (3) R^1R^2NH , R^1OH and R^1SH may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional
25 alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2a), (2b), (2c) and (2d) where appropriate functional groups exist in these compounds.

30

Thus intermediates of formula (3) may be obtained by hydrolysis of intermediates of formula (4):



where R^a represents a C_{1-6} alkyl group or a silyl group such as a t butyldimethylsilyl group.

5

The hydrolysis may be performed using an acid, for example an inorganic acid such as hydrochloric acid in an organic solvent such as an ether e.g. diethylether, or an alcohol e.g. ethanol optionally in the presence of added water at a temperature from about ambient to 80°C .

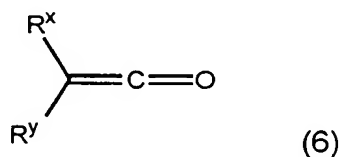
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Intermediates of formula (4) may be obtained by the cycloaddition of an intermediate of formula (5):



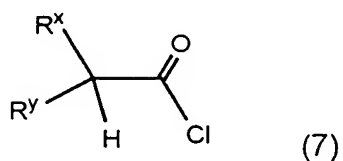
15

with a ketene of formula (6):



20

generated *in situ* during the cycloaddition reaction from an acid chloride of formula (7):



25

The reaction may be performed in the presence of an organic base such as an amine e.g. triethylamine or N,N -diisopropylethylamine or a cyclic

amine such as pyridine or N-methylmorphidine optionally in an organic solvent such as an ether e.g. diethylether or diisopopylether.

5 Acid chlorides of formula (7) may be obtained from the corresponding acids by a convenient method of generating acid halides, for example by reaction with thionyl chloride or oxalyl chloride under such standard conditions as are well known in the art.

10 Intermediate compounds of formula (4) may also be obtained from squaric acid derivations by such well known methods in the art as those of MacDougall, J. M. *et al*, J. Org. Chem, 64 5979-83 (1999); Hergueta, R. A., J. Org. Chem., 64, 5979-83, (1999); Heileman, M. J. *et al*, J. Am. Chem. Soc. 120, 3801-2, (1998); Yamamoto, Y. *et al*, J. Org. Chem, 62, 1292-8 (1997); Zhag, D. *et al*, J. Org. Chem. 61, 2594-5 (1996); Petasis, N. A. *et al*, Synlett, 155-6 (1996); Petasis, N. A. *et al*, Tetrahedron Lett., 36, 6001-4, (1995); Turnbull, P. *et al*, J. Org. Chem 60, 644-9 (1995); Yexa, B. R. *et al*, Tetrahedron, 50, 6173-80 (1994); Ezcurra, J. E. *et al*, Tetrahedron Lett, 34, 6177-80, (1993); Ohno, M. *et al*, Tetrahedron Lett., 34, 4807-10, (1993); Yexa, B. R. *et al*, Tetrahedron Lett. 33, 7811-14 (1992); Xu, S. L. *et al*, J. Org. Chem, 57, 326-8 (1992) and Kravs, J. L. *et al*, Tetrahedron Lett. 28, 1765-8 (1987).

25 Further compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a -L¹H or -L²H group (where L¹ and L² is each a linker atom or group) may be treated with a coupling agent R³(Alk¹)_nX¹ or Ar¹X¹ respectively in which X¹ is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

35 The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine, such as N-methylmorpholine or pyridine, in a dipolar aprotic solvent such

as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

5 Compounds of formula Ar^1X^1 may be prepared from alcohols of formula Ar^1OH by reaction with a halogenating agent, for example a phosphorous oxyhalide such as phosphorous oxychloride at an elevated temperature e.g. 110°C.

10 Intermediate alcohols of formula Ar^1OH in which, for example, Ar^1 represents a 2,6-naphthyridine may be prepared by methods well known to a person skilled in the art, e.g. by the method of Sakamoto, T. *et al* [Chem. Pharm. Bull. 33, 626-633, (1985)].

15 Alternatively alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a 2,6-naphthyridine may be prepared by reaction of a 2,6-naphthyridine N-oxide or N, N'-dioxide with a halogenating agent, e.g. a phosphorous oxyhalide such as phosphorous oxychloride to give a 1-halo or 1,5-dihalo-2,6-naphthyridine respectively. In the case of 1,5-dihalo-2,6-naphthyridines each halogen atom may be substituted separately by a
20 reagent such as $HL^2Ar^2AlkN(R^2)H$ or $HL^3(Alk^2)_tL^4(R^4)_u$ by the particular methods just described above.

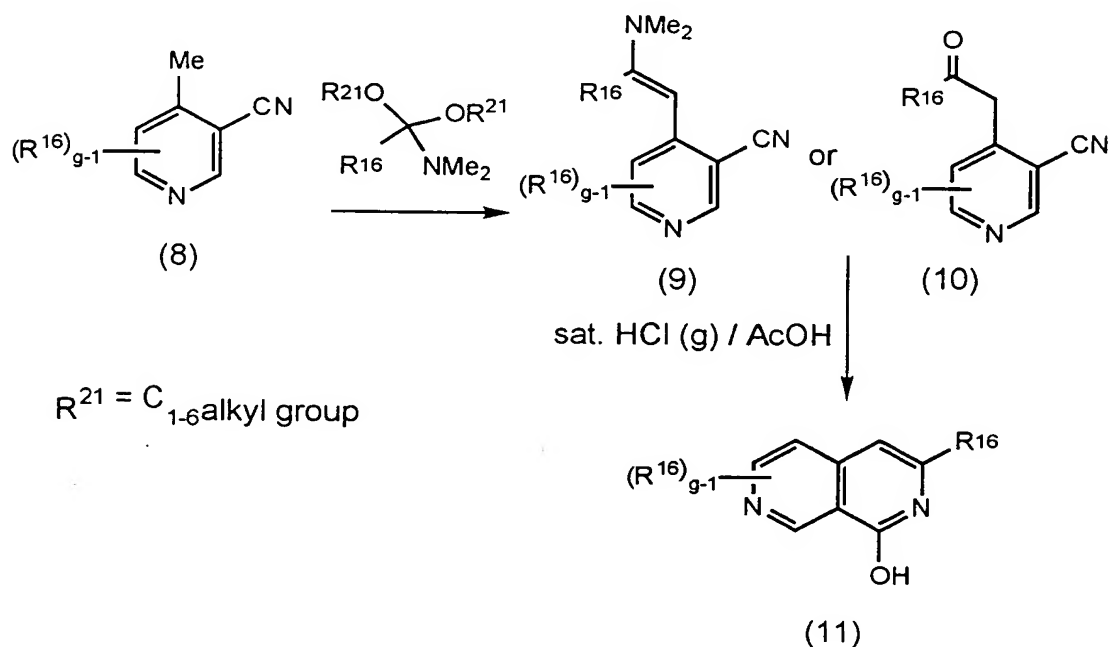
2,6-Naphthyridine N-oxides and N,N'-dioxides may be generated from the corresponding 2,6-naphthyridines by the general methods of synthesis of N-oxides described below or they may be synthesised by the methods of
25 Numata, A. *et al* (Synthesis, 1999, 306-311).

Further alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a 2,6-naphthyridine, may be prepared by the methods of
30 Giacomello G. *et al* [Tetrahedron Letters, 1117-1121 (1965)], Tan, R. and Taurins, A. [Tetrahedron Lett., 2737-2744, (1965)], Ames, D. E. and Dodds, W. D. [J. Chem. Soc. Perkin 1, 705-710 (1972)] and Alhaique, F. *et al* [Tetrahedron Lett., 173-174 (1975)].

35 Intermediate alcohols of formula Ar^1OH in which Ar^1 represents an optionally substituted 2,7-naphthyridin-1-yl group may be prepared by

methods well known to a person skilled in the art, e.g. by the method of Sakamoto, T. *et al* [Chem. Pharm. Bull. 33, 626-633, (1985)] or Baldwin, J. J. *et al* [J. Org. Chem, 43, 4878-4880, (1978)]. Thus for example the method of Baldwin may be modified to allow the synthesis of intermediate 3-substituted 2,7-naphthyridin-1-yl groups of formula Ar¹OH as depicted in Scheme 1:

Scheme 1



10

Reaction of an optionally substituted 4-methyl-3-cyano pyridine of formula (8) with a N,N-dimethylformamide di-C₁₋₆alkyl acetal, e.g. N,N-dimethylformamide diethyl acetal, in a dipolar solvent such as an amide e.g. a substituted amide such as dimethylformamide at an elevated temperature e.g. 140-150° gives a compound of formula (9) or (10) or a mixture thereof depending on the nature of the group R¹⁶.

15

Compounds of formula (9) or (10) may be cyclised to 3-substituted 2,7-naphthyridin-1-yl alcohol of formula (11) by treatment with an acid e.g. an inorganic acid such as hydrochloric acid or hydrobromic acid or an acidic gas such as hydrogen chloride gas in an organic solvent e.g. an organic

20

acid such as acetic acid optionally in the presence of water at a temperature from about ambient to 50°C.

Alternatively alkylating agents of formula Ar^1X^1 in which Ar^1 represents an optionally substituted 2,7-naphthyridin-yl group may be prepared by reaction of a 2,7-naphthyridine N-oxide or N, N'-dioxide with a halogenating agent, e.g. a phosphorous oxyhalide such as phosphorous oxychloride to give a 1-halo or 1,6-dihalo- and/or-1,8-dihalo-2,7-naphthyridine respectively. In the case of 1,6-dihalo- and/or 1,8-dihalo-2,6-naphthyridines each halogen atom may be substituted separately by a reagent such as $HL^2Ar^2AlkN(R^2)H$ or $HL^3(Alk^2)_tL^4(R^4)_u$ by the particular methods just described above.

2,7-Naphthyridine N-oxides and N,N'-dioxides may be generated from the corresponding 2,7-naphthyridines by the general methods of synthesis of N-oxides described below or they may be synthesised by the methods of Numata, A. *et al* (Synthesis, 1999, 306-311).

Further alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a 2,7-naphthyridin-1-yl, may be prepared by the methods of Wenkert E. *et al* J. Am. Chem. Soc. 89, 6741-5 (1967), and Aust. J. Chem. 433 (1972), and Sheffield D.J. J. Chem. Soc. Perkin. Trans I, 2506 (1972).

Intermediate alcohols of formula Ar^1OH in which Ar^1 represents a 3-substituted isoquinolin-1-yl group may be prepared by methods well known to a person skilled in the art, e.g. by the methods of Wu M.-J. *et al* Tetrahedron, 55, 13193-200 (1999), Hiebl J. *et al* Tetrahedron Lett. 40, 7935-8 (1999), Nagarajan A. *et al* Indian J. Chem., Sect. B, 28B, 67-78 (1989), Brun E. M. *et al* Synlett, 7, 1088-90 (1999) and Brun, E. M. *et al* Synthesis, 273-280 (2000).

Further alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a isoquinolin-1-yl group, may be prepared by the methods of Falk H. *et al* Monatsch. Chem. 25, 325-33 (1994), and Deady, L. W. *et al* Aust. J. Chem 42, 1029-34 (1989).

In a further example intermediates of formula R^1R^2NH may be obtained by reaction of a compound of formula Ar^1L^2H with a compound of formula $X^1Ar^2AlkN(R^2)H$ under the reaction conditions just described

5 Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 2,6-naphthyridine and L^2 is a $-N(R^8)-$ group, may be prepared from substituted 4-cyano-3-cyanomethylpyridines by the methods of Alhaique, F. *et al* (*ibid* and Gazz. Chim. Ital. 1975, 105, 1001-1009) or from 3-formylpyridines by the methods of Molina, P. *et al* (Tetrahedron 1992, 48, 4601-4616).

10

Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 2,7-naphthyridin-1-yl group and L^2 is a $-N(R^8)-$ group, may be prepared from substituted 4-formylpyridines by the methods of Molina, P. *et al* Tetrahedron, 48, 4601-4616, (1992), or by the methods described in US
15 3,938,367.

Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 3-substituted isoquinolin-1-yl group and L^2 is a $-N(R^8)-$ group, may be prepared by the methods of Bordner, J. *et al* J. Med. Chem. 31, 1036-9
20 (1988), Tovar J. D. *et al* J. Org. Chem., 64, 6499-6504 (1999), Karser E. M. *et al* Synthesis, 11, 805-6 (1974), and Molino, P *et al* J. Chem. Soc. Perkin Trans. 1 1727-31 (1990).

In another example, compounds containing a $-L^1H$ or $-L^2H$ or group as
25 defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^1 is replaced by a $-C(O)X^2$, $-C(S)X^2$, $-N(R^8)COX^2$ or $-N(R^8)C(S)X^2$ group in which X^2 is a leaving atom or group as described for X^1 . The reaction may be performed in the presence of a base, such as a hydride,
30 e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for
35 example one of the alkylating agents described above in which X^1 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for

example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a
 5 chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above
 10 alkylating agents but in which X¹ is replaced by a -S(O)Hal or -SO₂Hal group [in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

15 In another example, compounds containing a -L¹H or -L²H group as defined above may be coupled with one of the alkylation agents just described but in which X¹ is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine
 20 and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups -CO₂R⁵, -CO₂R¹¹ or -CO₂Alk⁷ in the compounds may be converted to the corresponding acid [-CO₂H] by acid-
 25 or base-catalysed hydrolysis depending on the nature of the groups R⁵, R¹¹ or Alk⁷. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

30 In a further example, -OR⁵ or -OR¹⁴ groups [where R⁵ or R¹⁴ each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g.
 35 dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding -OCH₂R¹⁴ group (where R¹⁴ is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or
 5 hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [CO₂Alk⁷ or CO₂R⁵] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

10

In another example, alcohol -OH groups in the compounds may be converted to a corresponding -OR⁵ or -OR¹⁴ group by coupling with a reagent R⁵OH or R¹⁴OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as
 15 diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [-NHSO₂NHR³ or -NHSO₂NHAr¹] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [-NH₂] with a sulphamide R³NHSO₂NH₂ or
 20 Ar¹NHSO₂NH₂ in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a -NHCSAr¹, -CSNHAr¹, -NHCSR³ or -CSNHR³ may be prepared by treating a corresponding
 25 compound containing a -NHCOAr¹, -CONHAr¹, -NHCOR³ or -CONHR³ group with a thiation reagent, such as Lawesson's Reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

30 In a further example amine (-NH₂) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in
 35 the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [-NH₂] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L¹ or L² may be oxidised to the corresponding sulfoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In another example compounds of formula Ar¹X¹ (where X¹ is a halogen atom such as a chlorine, bromine or iodine atom) may be converted to such compounds as Ar¹CO₂R²⁰ (in which R²⁰ is an optionally substituted alkyl, aryl or heteroaryl group), Ar¹CHO, Ar¹CHCHR²⁰, Ar¹CCR²⁰, Ar¹N(R²⁰)H, Ar¹N(R²⁰)₂, for use in the synthesis of for example compounds of formula Ar¹L²Ar²AlkN(R²)H, using such well known and commonly used palladium mediated reaction conditions as are to be found in the general reference texts *Rodd's Chemistry of Carbon Compounds*,

- Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), *Fieser and Fieser's Reagents for Organic Synthesis*, Volumes 1-19 (John Wiley and Sons, 1999), *Comprehensive Heterocyclic Chemistry*, Ed. Katritzky *et al*, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon),
- 5 *Comprehensive Organic Functional Group Transformations*, Ed. Katritzky *et al*, Volumes 1-7, 1995 (Pergamon), *Comprehensive Organic Synthesis*, Ed. Trost and Fleming, Volumes 1-9, (Pergamon, 1991), *Encyclopedia of Reagents for Organic Synthesis*, Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), *Larock's Comprehensive Organic Transformations* (VCH
- 10 Publishers Inc., 1989) and *March's Advanced Organic Chemistry* (John Wiley and Sons, 1992).

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such

15 as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

20 Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

25 Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

30 Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment

35 with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively,
 5 a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

10 Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in
 15 °C. The following abbreviations are used:

NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
MeOH - methanol;	BOC - butoxycarbonyl;
DCM - dichloromethane;	AcOH - acetic acid;
DIPEA - diisopropylethylamine;	EtOH - ethanol;
20 Pyr - pyridine;	Ar - aryl;
DMSO - dimethylsulphoxide;	iPr - isopropyl;
Et ₂ O - diethylether;	Me - methyl;
THF - tetrahydrofuran,	DMF - N,N-dimethylformamide;
Fmoc - 9-fluorenylmethoxycarbonyl;	
25 DBU - 1,8-Diazabicyclo[5,4-0]undec-7-ene	

All NMR's were obtained either at 300MHz or 400MHz.

INTERMEDIATE 1

(+/-) 3-Ethoxy-4-methyl-4-propyl- 2-cyclobuten-1-one.

30 The title compound was prepared using a modification of the method of Wasserman, H.H. *et al* [J. Org. Chem, 38, 1451-1455, (1973)]; to a solution of 2-methyl pentanoyl chloride (3.91ml) and ethyl ethynylether (5g, 40% solution in hexanes, 28.6mmol) in Et₂O (35ml) at room temperature
 35 was added triethylamine (9.9ml), with stirring. The reaction was warmed to 50° and stirred for 72h prior to cooling and filtration. The filtrate was

concentrated *in vacuo* and the residual oil chromatographed (SiO₂; hexanes 80: EtOAc 20) to give the title compound as a colourless oil (3.71g, 17.9mmol, 77%). δ H (CDCl₃, 300K), 4.84 (1H, s), 4.24-3.98 (2H, m), 2.04 (3H, s), 1.56-1.43 (4H, m), 1.30-1.26 (3H, m), 0.91 (3H, t, \downarrow 7.3Hz). m/z (ES⁺, 70V) 178.1 (MH⁺).

INTERMEDIATE 2

(+/-) 3-Hydroxy-4-methyl-4-propyl- 2-cyclobuten-1-one

Intermediate 1 (1g, 59.5mmol) and conc. hydrochloric acid (2ml) were stirred vigorously at room temperature for 48h. The resulting slurry was filtered and the residue washed with water (3 x10ml) and dried under vacuum to give the title compound as an off-white powder (620mg, 44.2mmol, 74%). δ H (CDCl₃, 300K) 3.79 (2H, s), 1.59-1.53 (2H, m), 1.41-1.27 (2H, m), 1.18 (3H, s), 0.85 (3H, t, \downarrow 7.3Hz). m/z (ES⁺, 70V) 140.9 (MH⁺).

INTERMEDIATE 3

3-Ethoxy-4,4-dipropyl-2-cyclobuten-1-one.

The title compound was prepared using a modification of the method of Wasserman, H.H. *et al*, [J. Org. Chem, 38, 1451-1455, (1973)]; triethylamine (29ml) was added dropwise at room temperature to a well-stirred solution of di-n-propylacetyl chloride (13.9g, 85.8mmol) and ethyl ethynylether (15g, 40% solution in hexanes, 85.7mmol) in toluene (120ml). The reaction was warmed to 60° and stirred for 48h prior to cooling and filtration. The filtrate was concentrated *in vacuo* and the residual oil chromatographed (SiO₂; hexanes 80: EtOAc 20) to give the title compound as a brown oil (11.2g, 57.1mmol, 67%). δ H (CDCl₃, 300K) 5.02 (1H, s), 4.32 (2H, q, \downarrow 7.1Hz), 1.69-1.61 (4H, m), 1.45-1.40 (4H, m), 1.02 (6H, t, \downarrow 7.3Hz). m/z (ES⁺, 70V) 197.1 (MH⁺).

INTERMEDIATE 4

3-Hydroxy-4,4-dipropyl-2-cyclobuten-1-one

Intermediate 3 (10.2mmol) and 6M hydrochloric acid (10ml) were stirred vigorously at 65° for 72h. The resulting slurry was diluted with DCM (30ml) and distilled water (30ml) and extracted with DCM (3x10ml). The combined extracts were dried (MgSO₄), filtered and concentrated *in vacuo*

to give the title compound as a pale yellow oil, which crystallised on standing (1.49g, 8.87mmol, 87%).

INTERMEDIATE 5

3-Ethoxy-2-hexyl-4,4-dimethyl-2-cyclobuten-1-one.

The title compound was prepared using a modification of the method of Wasserman, H.H. *et al*, [J. Org. Chem, 38, 1451-1455, (1973)]; triethylamine (22ml) was added dropwise at room temperature to a well-stirred solution of isobutyryl chloride (7.3ml, 69mmol) and 1-ethoxy-1-octyne [prepared according to the method of Kocienski, P. *et al*. Tetrahedron Lett. 1833, 30, (1989)] (6.5g, 63mmol) in diethylether (100ml). The reaction was warmed to 35° and stirred for 96h prior to cooling and filtration. The filtrate was concentrated *in vacuo* and the residual oil chromatographed (SiO₂; hexanes 80: EtOAc 20) to give the title compound as a brown oil (8.6g, 38mmol, 61%). δ H (CDCl₃, 300K) 4.34 (2H, d, J 7.1Hz), 2.05 (2H, dd, \downarrow 5.6Hz 7.3Hz), 1.44 (3H, t, \downarrow 7.1Hz), 1.27-1.12 (8H, m), 1.23 (6H, s), 0.89 (3H, t, \downarrow 2.7Hz). m/z (ES⁺, 70V) 225.0 (MH⁺).

INTERMEDIATE 6

2-Hexyl-3-hydroxy-4,4-dimethyl-2-cyclobuten-1-one.

Intermediate 5 (7.6g, 34.0mmol) and 6M hydrochloric acid (10ml) were stirred vigorously at 100° for 18h. The resulting slurry was diluted with DCM (30ml) and distilled water (30ml) and extracted with DCM (3 x 10ml). The combined extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was triturated with hexanes and filtered to give the title compound as an off-white powder (6.5g, 33.0mmol, 98%). δ H (CDCl₃, 300K) 2.01 (2H, t, \downarrow 7.0Hz), 1.49-1.44 (2H, m), 1.34-1.19 (14H, m), 0.89-0.84 (3H, m). m/z (ES⁺, 70V) 197.0 (MH⁺).

INTERMEDIATE 7

(+/-) 4-Benzyl-3-ethoxy-4-methyl-2-cyclobuten-1-one

The title compound was prepared using a modification of the procedure of Wasserman *et al* [J. Org. Chem, 38, 1451-1455, (1973)]; triethylamine (20ml) was added to a stirred solution containing α -methyl tetrahydro-cinnamoyl chloride (5g, 27.5mmol) and ethyl ethynylether (6g, 40% soln. in

hexanes, 85.7mmol) and the resulting slurry heated to 35° for 3d. The crude reaction mixture was then filtered and the residue concentrated *in vacuo*. The residual oil was chromatographed (SiO₂, EtOAc 20: hexanes 80) to give the title compound as a pale brown oil (4.91g, 86%). δ H (CDCl₃, 300K) 7.19-7.05 (5H, m), 4.56 (1H, s), 4.09-4.00 (1H, m), 3.97-3.89 (1H, m), 2.86 (1H, d, \downarrow 14.0Hz), 2.86 (1H, d, \downarrow 14.0Hz), 1.30 (3H, t, \downarrow 7.1Hz), 1.24 (3H, s). m/z (ES⁺, 70V) 216.9 (MH⁺).

INTERMEDIATE 8

(+/-) 4-Benzyl-3-hydroxy-4-methyl-2-cyclobuten-1-one.

Intermediate 7 (4.5g, 20.9mmol) and hydrochloric acid (6M, 10ml) were stirred at room temperature for 48h. Filtration of the resulting slurry and washing of the residue with water (3 x 15ml) gave the title compound as a pale brown powder (3.92g, 20.8mmol, 99%). δ H (CDCl₃, 300K) 7.03-6.83 (5H, m), 4.24 (1H, s), 2.52 (2H, s), 0.94 (3H, s). m/z (ES⁺, 70V) 189.1 (MH⁺).

INTERMEDIATE 9

3-Cyanopyridinyl-4-(2-(N,N-dimethylamino)ethylen-1-yl)

A solution of 4-methyl-3-cyanopyridine [prepared according to Ref: J. Prakt. Chem. 338, 663 (1996)], (8.0g, 67.8mmol) and *N,N*-dimethylformamide diethyl acetal (11.0g, 74.8mmol) in dry DMF (50ml) was stirred at 140° under N₂ for 2 days. An additional portion of *N,N*-dimethylformamide diethyl acetal (5g) was added and stirred at 140° for 4h. The volatiles were removed *in vacuo* and the obtained dark oil partitioned between EtOAc (300ml) and water (50ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 100ml). The combined organic extracts were washed with brine (30ml), dried (Na₂SO₄), treated with activated charcoal, filtered and evaporated *in vacuo* to afford essentially pure title compound as a dull orange solid (10.1g, 85%). δ H (CDCl₃) 8.49 (1H, s), 8.25 (1h, d, \downarrow 5.9hz), 7.29 (1H, d, \downarrow 13.2Hz), 7.09 (1H, d, \downarrow 5.9Hz), 5.25 (1H, d, \downarrow 13.2Hz) and 2.99 (6H, s); m/z (ES⁺, 70V) 174 (MH⁺).

INTERMEDIATE 10

1-Hydroxy-2,7-naphthyridine hydrochloride salt

HCl gas was bubbled through a stirred solution of Intermediate 9 (6.2g, 3.58mmol) in glacial acetic acid (50ml) and water (0.64ml, 3.55mmol) for 1-2min. The reaction mixture was stirred in a stoppered flask at 40° for 18h. The volatiles were removed *in vacuo* affording a dark residue, which was treated with water (3 x 20ml) and re-evaporated *in vacuo*. The obtained dark semi-solid was treated with 40ml warm ethanol, ice-cooled, and the undissolved solid collected by filtration affording the title compound as a green coloured solid (5.2g, 80%) δ H (DMSO- d_6) 12.5 (1H, br s), 9.38 (1H, s), 8.84 (1H, d, \downarrow 7.0Hz), 8.15 (1H, d, \downarrow 7.0Hz), 7.89 (1H, br dd, \downarrow 7.0, 5.0Hz) and 6.85 (1H, d, \downarrow 7.0Hz); m/z (ES⁺, 70V), 147 (MH⁺).

INTERMEDIATE 11

1-Chloro-2,7-naphthyridine

Intermediate 10 (5.2g, 28.5mmol) was stirred with phosphorous oxychloride (75ml) at 110° for 24h. The volatiles were removed *in vacuo* affording a dark oil which was poured into an ice-bath cooled mixture of saturated aqueous NaHCO₃ (100ml containing 20g solid NaHCO₃) and EtOAc (100ml). After thorough mixing the phases were separated and the aqueous layer re-extracted with EtOAc (2 x 75ml). The combined organic extracts were washed with brine (15ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as a yellow solid (4.0g, 85%) δ H (CDCl₃) 9.45 (1H, s), 8.81 (1H, d, \downarrow 5.7HZ), 8.47 (1H, d, \downarrow 5.7Hz), 7.66 (1H, d, \downarrow 5.7Hz) and 7.60 (1H, d, \downarrow 5.7HZ); m/z (ES⁺, 70V) 165 and 167 (MH⁺).

INTERMEDIATE 12

Ethyl (2S)-2-amino-3-[4-(2,7-naphthyridin-1-ylamino)phenyl]propanoate

A solution of ethyl-(S)-3-[4-aminophenyl]-2-[*t*-butoxycarbonylamino]propanoate (638mg, 2.07mmol) and Intermediate 11 (310mg, 1.88mmol) in ethoxyethanol (2ml) was stirred at 120° for 15 min and at 100° for 1h under nitrogen. The volatiles were removed *in vacuo* and the dark residue partitioned between EtOAc (70ml) and saturated aqueous NaHCO₃ (10ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford a dark

foam. Chromatography (SiO₂; 5 to 10% MeOH/DCM) afforded a mixture of ethyl-(S)-3-[4-(2,7-naphthyridin-1-ylamino)phenyl]-2-[(*t*-butoxycarbonyl)amino]propanoate and some of the title compound (730mg). This mixture was treated with a solution of trifluoroacetic acid (5ml) and DCM (5ml) at room temperature for 1h. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (75ml) and saturated aqueous NaHCO₃ (20ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford an orange solid. Chromatography (silica; 10% MeOH/DCM) afforded the title compound as a straw-coloured solid (420mg, 60% over two steps). δ H (CDCl₃) 10.70 (1H, s), 10.31 (1H, s), 9.44 (1H, d, \downarrow 5.6Hz), 8.94 (1H, d, \downarrow 5.6Hz), 8.55 (1H, d, \downarrow 7.3Hz), 8.54 (2H, d, \downarrow 8.5Hz), 8.46 (1H, d, \downarrow 5.6Hz), 7.94 (2H, d, \downarrow 8.5Hz), 4.84 (2H, q, \downarrow 7.1Hz), 4.35 (1H, t, \downarrow 6.6Hz), 4.10 (2H, br s), 3.64 (1H, dd, \downarrow 13.5, 6.4Hz), 3.56 (1H, dd, \downarrow 13.5, 7.0Hz) and 1.95 (3H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 337 (MH⁺).

INTERMEDIATE 13

Methyl (2S)-2-amino-3-[4-(2,7-naphthyridin-1-yloxy)phenyl]propanoate

A mixture of *N*-(BOC)-(S)-tyrosine methyl ester (1.71g, 5.80 mmol) potassium carbonate (0.80g, 5.80mmol) and Intermediate 11 (1.0g, 6.08mmol) in dry DMF (10ml) was stirred at room temperature for 18h, and at 40° for 18h. The DMF was removed *in vacuo* and the residue partitioned between EtOAc (80ml) and 10% aqueous Na₂CO₃ (20ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford a new colourless oil. Chromatography (silica; 2.5% MeOH/DCM) afforded reasonably pure *N*-*t*-butoxycarbonyl protected title compound (1.75g, 71%). This material was dissolved in EtOAc (40ml) and HCl gas was bubbled through the stirred solution for 1min. then the mixture was stirred for an additional 0.5h. The volatiles were removed *in vacuo* affording a yellow solid which was partitioned between EtOAc (80ml) and saturated aqueous NaHCO₃ (20ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo*. The obtained oil

was chromatographed (silica; 5% MeOH/DCM) to afford the title compound as a near colourless oil (0.83g, 62%) δ H (CDCl₃) 9.77 (1H, s), 8.75 (1H, d, \downarrow 5.8Hz), 8.10 (1H, d, \downarrow 5.8Hz), 7.58 (1H, d, \downarrow 5.8Hz), 7.29 (2H, d, \downarrow 8.4Hz), 7.25 (1H, d, \downarrow 5.9Hz), 7.21 (2H, d, \downarrow 8.4Hz), 3.80-3.70 (1H, obscured m), 3.72 (3H, s), 3.15 (1H, dd, \downarrow 13.6, 5.1Hz), 2.88 (1H, dd, \downarrow 13.6, 8.0Hz) and 0.78 (2H, br s); m/z (ES⁺, 70V) 324 (MH⁺).

INTERMEDIATE 14

4-Acetyl-3-cyanopyridine

10 A solution of 4-methyl-3-cyanopyridine (4g, 33.9mmol) and *N,N*-dimethylacetamide dimethylacetyl (5.4g, 40.6mmol) in dry DMF (20ml) was stirred at 130° for 7h. The volatiles were removed *in vacuo* to afford a dark oil which solidified on standing. This material was chromatographed (silica; 50% EtOAc/ Hexane - 100% EtOAc) affording the title compound
15 as an off-yellow solid (3.73g, 69%). δ H (CDCl₃) 8.87 (1H, s), 8.74 (1H, d, \downarrow 5.2Hz), 7.28 (1H, d, \downarrow 5.2Hz), 4.00 (2H, s) and 2.36 (3H, s); m/z (ES⁺, 70V) 161 (MH⁺).

INTERMEDIATE 15

1-Hydroxy-3-methyl-2,7-naphthyridine hydrochloride

20 HCl gas was bubbled through a stirred solution of Intermediate 14 (3.73g, 23.3mmol) in glacial acetic acid (40ml) for several minutes. The flask was stoppered and reaction stirred for 18h at ambient temperature. The volatiles were removed *in vacuo* affording a straw-coloured solid. This
25 was twice treated with water (30ml portions) and re-evaporated *in vacuo* to dryness, affording the title compound (contaminated with ~25% unidentified by-product) as a dark straw coloured solid (4.1g). δ H (DMSO-d₆) 12.46 (1H, br s), 9.32 (1H, s), 8.71 (1H, d, \downarrow 6.5Hz), 7.98 (1H, d, \downarrow 6.5Hz), 6.67 (1H, s) and 2.38 (3H, s); m/z (ES⁺, 70V) 161 (MH⁺). Used
30 without further purification.

INTERMEDIATE 16

1-Chloro-3-methyl-2,7-naphthyridine

Intermediate 15 (4.1g) was treated with phosphorus oxychloride (50ml) at
35 130° for 3h, affording a dark solution. The volatiles were removed *in vacuo* and the obtained dark oil extracted with Et₂O (100ml). Saturated

aqueous NaHCO₃ (ice cold; containing 10g additional solid NaHCO₃) was poured (with CARE!) onto the crude product with swirling and ice-bath cooling. After thorough shaking, addition Et₂O (80ml) was added, the mixture re-shaken, and the phases separated. The aqueous layer was re-extracted with Et₂O (2 x 80ml) and the combined ethereal extracts washed with brine (20ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford an orange solid (3.6g). Chromatography (silica; 70% EtOAc/Hexane - 100% EtOAc) afforded a more-polar by-product (3-methyl-1H-pyrano[3,4-C]pyridin-1-one, (0.7g) and the title compound as a white solid (2.82g, 79% from intermediate 7) δ H (CDCl₃) 9.66 (1H, s), 8.73 (1H, d, \downarrow 5.8hz), 7.56 (1H, d, \downarrow 5.8Hz), 7.40 (1H, s) and 2.69 (3H, s); m/z (ES⁺, 70V) 179 and 181 (MH⁺).

INTERMEDIATE 17

Ethyl (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-{4-[(3-methyl[2,7-naphthyridin-1-yl]amino]phenyl}propanoate hydrochloride

Acetylchloride (55mg, 50ml, 0.70mmol) was added to absolute ethanol (25ml) and stirred for one minute. Intermediate 16 (2.50g, 14.0mmol) and ethyl-(S)-3-[4-aminophenyl]-2-{*tert*-butyloxycarbonyl}propanoate (4.31g, 14.0mmol) were added and the reaction mixture stirred at 60° for 2.75h. The volatiles were removed *in vacuo* to afford a yellow-orange solid. This was treated with EtOAc (~25ml), warmed, re-cooled and the precipitate collected by filtration, with Et₂O washing, affording the title compound as yellow solid (4.96g, 73%). δ H (CDCl₃) 10.44 (1h, br s), 10.33 (1H, br s), 8.60 (1H, d, \downarrow 6.5Hz), 8.00 (1H, d, \downarrow 6.5Hz), 7.85 (2H, d, \downarrow 8.5Hz), 7.28 (1H, d, \downarrow 8.0Hz), 7.23 (2H, d, \downarrow 8.5Hz), 7.16 (1H, s), 4.19-4.01 (1H, m), 4.08 (2H, q, \downarrow 7.0Hz), 2.97 (1H, dd, \downarrow 13.8, 5.4 Hz), 2.86 (1H, dd, \downarrow 13.8, 10.0Hz), 2.50 (3H, s), 1.34 (9H, s) and 1.15 (3H, t, \downarrow 7.0Hz); m/z (ES⁺, 70V) 451 (MH⁺).

INTERMEDIATE 18

Ethyl-(2S)-2-amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)amino]phenyl}propanoate

HCl gas was bubbled through a stirred solution of Intermediate 17 (4.95g, 10.2mmol) for 1-2min. After 30min stirring at ambient temperature the volatiles were removed *in vacuo* affording a yellow powder. This was

treated with saturated aqueous NaHCO_3 (30ml) then extracted with EtOAc (100ml, and 3 x 50ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* affording the title compound as a yellow solid (3.56, 100%). δH (CDCl_3) 9.25 (1H, s), 8.50 (1H, d, \downarrow 5.6Hz), 7.66 (2H, d, \downarrow 8.4Hz), 7.35 (1H, d, \downarrow 5.6Hz), 7.34 (1H, masked s), 7.14 (2H, d, \downarrow 8.4Hz), 6.81 (1H, s), 4.12 (2H, q, \downarrow 7.2Hz), 3.65 (1H, dd, \downarrow 7.8, 5.2Hz), 3.02 (1H, dd, \downarrow 13.7, 5.2Hz), 2.80 (1H, dd, \downarrow 13.7, 7.8Hz), 2.48 (3H, s), 1.56 (2H, br s) and 1.21 (3H, t, \downarrow 7.2Hz); m/z (ES^+ , 70V) 351 (MH^+).

10

INTERMEDIATE 19

Ethyl (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

A mixture of *N*-*t*-butoxycarbonyl-(*S*)-tyrosine ethyl ester (14.5g, 46.9mmol), caesium carbonate (14.05g, 43.1mmol) and Intermediate 9 (7.0g, 39.2mmol) in dry DMF (60ml) was stirred at room temperature for 48h. The reaction was diluted with Et_2O (150ml) and filtered off. The filtrate was evaporated under high vacuum and the residue was chromatographed (SiO_2 ; 40% - 60% EtOAc/Hexane) which afforded the title compound as a viscous, straw-coloured oil (16.2g, 77%) δH (CDCl_3) 9.56 (1H, s), 8.58 (1H, d, \downarrow 5.8Hz), 7.39 (1H, d, \downarrow 5.8Hz), 7.15-7.10 (4H, m), 7.00 (1H, s), 4.99-4.91 (1H, m), 4.54-4.46 (1H, m), 4.09 (2H, q, \downarrow 7.1Hz), 3.10-2.99 (2H, m), 2.36 (3H, s), 1.34 (9H, s) and 1.15 (3H, t, \downarrow 7.1Hz); m/z (ES^+ , 70V) 452 (MH^+).

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INTERMEDIATE 20

Ethyl (2S)-2-amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

HCl gas was bubbled through a stirred solution of Intermediate 19 (16g) in EtOAc (300ml) until a persistent fine white precipitate formed (~2minutes). After stirring for 0.5h the volatiles were removed *in vacuo*. The obtained solid was partitioned between EtOAc (250ml) and saturated aqueous NaHCO_3 (80ml plus 5g solid NaHCO_3). The phases were separated and the aqueous layer re-extracted with EtOAc (5 x 50ml). The combined organic extracts were washed with brine (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford an oil. Chromatography (SiO_2 ; 100%

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EtOAc - 10% EtOH/EtOAc) afforded the title compound as a viscous oil (11.1g, 89%). δ H (CDCl₃) 9.71 (1H, s), 8.70 (1H, d, \downarrow 5.8Hz), 7.50 (1H, d, \downarrow 5.8Hz), 7.31-7.28 (4H, m), 7.11 (1H, s), 4.23 (2H, q, \downarrow 7.1Hz), 3.79-3.72 (1H, m), 3.14 (1H, dd, \downarrow 14.1, 5.4Hz), 2.94 (1H, dd, \downarrow 14.1, 7.8Hz), 2.47 (3H, s), 1.75-1.50 (2H, br s) and 1.30 (3H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 352 (MH⁺).

INTERMEDIATE 21

1-Chloro-2,6-naphthyridine

10 1-Hydroxy-2,6-naphthyridine (550mg) [prepared according to the method of Sakamoto, T. *et al* Chem. Pharm. Bull. 33, 626, (1985)] was stirred with phosphorous oxychloride (10ml) at 110° for 5h. The volatiles were removed *in vacuo* and the residue treated carefully with ice. After diluting with water (to ~25ml), solid NaHCO₃ was added to effect neutralisation and the product extracted into EtOAc (2 x 80ml). The combined organic extracts were dried (MgSO₄), evaporated *in vacuo*, and the crude product chromatographed (SiO₂; EtOAc) affording the title compound as a slightly yellow solid (420mg, 68%). δ H (CDCl₃) 9.35 (1H, s), 8.82 (1H, d, \downarrow 5.9Hz), 8.48 (1H, d, \downarrow 5.6Hz), 8.00 (1H, d, \downarrow 5.9Hz), 7.74 (1H, d, \downarrow 5.6Hz); m/z (ES⁺, 70V) 165 and 167 (MH⁺).

INTERMEDIATE 22

Ethyl (2S)-2-[(*tert*-butoxycarbonyl)amino]3-[4-[(2,6)naphthyridin-1-ylamino]phenyl]propanoate

25 Ethyl (S)-3-(4-aminophenyl)-2-[N-(*t*-butyloxycarbonyl)amino]propanoate (600mg, 1.95mmol), Intermediate 21 (350mg, 2.13mmol) and DIPEA (276mg, 372 μ l, 2.13mmol) in 2-ethoxyethanol (0.5ml) were stirred at 130° under N₂ for several hours. The reaction was partitioned between EtOAc (70ml) and saturated aqueous NaHCO₃ (30ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were washed with brine (10ml), dried (MgSO₄) and evaporated *in vacuo* to afford a dark oil. Chromatography (SiO₂; 3% MeOH/DCM) gave the title compound as a dull orange foam (360mg, 42%). δ H (CDCl₃) 9.19 (1H, s), 8.67 (1H, d, \downarrow 5.9Hz), 8.24 (1H, d, \downarrow 5.8Hz), 7.66 (1H, d, \downarrow 5.9Hz), 7.65 (2H, d, \downarrow 8.5Hz), 7.21 (1H, d, \downarrow 5.8Hz), 7.16 (2H, d, \downarrow 8.5Hz), 7.15 (1H, obscured s), 5.05-4.97 (1H, m), 4.60-4.51

(1H, m), 4.19 (2H, q, \downarrow 7.1Hz), 3.17-3.04 (2H, m), 1.44 (9H, s), 1.27 (3H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 459 (MNa⁺), 437 (MH⁺).

INTERMEDIATE 23

5 Ethyl (2S)-2-amino-3-[4-([2.6]naphthyridin-1-ylamino)phenyl]propanoate

Intermediate 22 (360mg) was treated with a solution of trifluoroacetic acid (10ml) and DCM (10ml) and stirred at RT for 2h. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (80ml) and saturated aqueous NaHCO₃ (30ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were dried (MgSO₄) and evaporated *in vacuo* to afford the title compound as a dark orange viscous oil (280mg, 100%). δ H (CDCl₃) 9.18 (1H, s), 8.66 (1H, d, \downarrow 5.9Hz), 8.22 (1H, d, \downarrow 5.8Hz), 7.67 (1H, d, \downarrow 5.9Hz), 7.64 (2H, d, \downarrow 8.5Hz), 7.22 (2H, d, \downarrow 8.5Hz), 7.19 (1H, d, \downarrow 5.8Hz), 4.20 (2H, q, \downarrow 7.1Hz), 3.73 (1H, dd, J 7.9, 5.1Hz), 3.10 (1H, dd, \downarrow 13.6, 5.2Hz), 2.87 (1H, dd, \downarrow 13.6, 7.9Hz), 1.70 (3H, br s), 1.28 (3H, t, 7.1Hz); m/z (ES⁺, 70V) 337 (MH⁺).

20 INTERMEDIATE 24

Methyl (2S)-2-(*t*-tert-butoxycarbonyl)amino]-3-[4-([2.6]naphthyridin-1-yl)oxy]phenyl]propanoate

To *N*-(*t*-butoxycarbonyl)(*S*) tyrosine methyl ester (1.42g, 4.82mmol) in dry DMF (10ml) was added Intermediate 21 (0.79g, 4.82mmol) and cesium carbonate (1.65g, 5.06 mmol) and the reaction stirred at 45° under N₂ for 2 days. The DMF was evaporated, EtOAc added and washed (3x) with water, dried (MgSO₄), and evaporated *in vacuo*. The residue was chromatographed (SiO₂; 40 to 100% EtOAc/isohexane) to afford the title compound as white foam (1.61g, 82%). δ H (CDCl₃) 9.29 (1H, s), 8.76 (1H, d, \downarrow 5.74HZ), 8.17 (1H, d, \downarrow 5.74Hz), 8.11 (1H, d, \downarrow 5.8Hz), 7.43 (1H, d, \downarrow 5.8Hz), 7.22-7.18 (3H, m), 5.03 (1H, br s), 4.61 (1H, br s), 3.75 (3H, s), 3.15-3.05 (2H, m), 1.44 (9H, s); m/z (ES⁺, 70V) MH⁺ 424.

INTERMEDIATE 25

35 3,5-Dichloropyridine-4-carboxylic acid

A solution of 3,5-dichloropyridine (5.00g, 33.8mmol) in THF (25ml) was added to a solution of LDA [generated from nBuLi (2.5M solution in hexanes, 14.9ml, 37.2mmol) and diisopropylamine (4.10g, 5.7ml, 40.6mmol)] in THF (25ml) at -78° under nitrogen, to give a yellow/brown slurry. The reaction was stirred for 30min at -78° then CO₂ gas was bubbled through to give a clear brown solution that slowly gave a precipitate, warmed to RT over 2h, then quenched with water (20ml) and partitioned between Et₂O (100ml) and 1M NaOH (100ml). The aqueous layer was separated and acidified to pH1 with concentrated hydrochloric acid and then extracted with 10% MeOH in DCM (100ml x 3). The combined organic layers were dried (MgSO₄) and the solvent removed under vacuum to give a brown solid that was recrystallised from ethanol and dried under vacuum to give the title compound as pinkish crystals (2.63g, 41%). δH (DMSO-d₆) 8.74 (2H, s). δC (DMSO-d₆) 163.5, 147.7, 141.0, 126.7

INTERMEDIATE 26

Ethyl (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate

A slurry of the compound of Intermediate 25 (51.2g, 0.267mol) in DCM (195ml) and thionyl chloride (195ml, 2.67mol) was treated with DMF (5 drops) and heated to reflux for 4h. The reaction was concentrated *in vacuo* and azeotroped with toluene (2 x 50ml) to give a yellow solid which was used without further purification. A solution of ethyl-(S)-3-(4-aminophenyl)-2-(*t*-butoxycarbonyl amino)propionate (130.8g, 0.425mol) in DCM (800ml) was cooled to 0° and treated with NMM (56.0ml, 0.51mol), stirred 5 minutes and then a solution of the acid chloride (98.3g, 0.468mol) in DCM (200ml) was added dropwise keeping the reaction temperature below 5°. The reaction was stirred for 1h, quenched with NaHCO₃ solution (500ml), the organic layer separated, washed with NaHCO₃ solution (500ml), 10% citric acid solution (500ml) and NaHCO₃ solution (500ml), dried (MgSO₄) and concentrated *in vacuo* to give a yellow solid which was recrystallised (EtOAc/hexane) to give the title compound, (140g, 69%). δH (DMSO d₆), 8.8 (2H, s), 7.55 (2H, d, *J* 8.5Hz), 7.23 (2H, d, *J* 8.5Hz), 4.0 (3H, m), 3.4 (2H, b s), 2.9 (1H, m), 2.8 (1H, m), 1.3 (9H, s), 1.25 (3H, t). m/z (ES⁺, 70V) 504 (MNa⁺).

INTERMEDIATE 27**Ethyl (2S)-2-amino-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate hydrochloride**

- 5 A solution of the compound of Intermediate 26 (70g, 0.146mol) in EtOAc (500ml) and 1,4-dioxan (50ml) was treated with a solution of HCl in EtOAc (500ml, 3M), and stirred at RT for 4h. The reaction was concentrated *in vacuo* to give a yellow solid which was triturated with Et₂O then recrystallised (EtOAc/hexane) to give the title compound (59.3g, 92%).
- 10 δ H (DMSO d₆), 11.10 (1H, s), 8.70 (2H, s), 7.55 (2H, d, \downarrow 8.4Hz), 7.25 (2H, d, \downarrow 8.4Hz), 4.10 (3H, m), 3.10 (2H, m), 1.10 (3H, m). m/z (ES⁺, 70V) 382 (MH⁺).

EXAMPLE 1

- 15 **Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-[4-[(2,7)naphthyridin-1-yloxy]phenyl]propanoate**

A solution of 3-ethoxy-4,4-dimethyl-2-cyclobutenone (57mg, 0.51mmol) [prepared according to the method of Wasserman, H.H. *et al* J. Org. Chem, 38, 1451-1455, (1973)] and the ethyl ester prepared according to

20 the method used to prepare Intermediate 13 (164mg, 0.51mmol), in 1,2-dichloroethylene (5ml), was stirred at room temp. for 72h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO₂; EtOAc) affording the title compound as a white solid (188mg, 0.45mmol, 89%). δ H (CDCl₃, 300K) 9.92 (1H, s), 8.75 (1H, d, \downarrow 5.7Hz), 8.60 (1H, d, \downarrow 8.6Hz),

25 8.04 (1H, d, \downarrow 5.8Hz), 7.82 (1H, d, \downarrow 5.6Hz), 7.47 (1H, d, \downarrow 5.8Hz), 7.27 (2H, d, \downarrow 8.5Hz), 7.16 (2H, d, \downarrow 8.5Hz), 4.31 (1H, s), 4.30-4.21 (1H, m), 3.68-3.63 (2H, q, \downarrow 7.1Hz), 3.17 (1H, dd, \downarrow 13.6, 9.4Hz), 2.95 (1H, dd, \downarrow 5.0, 13.6Hz), 1.01 (3H, s), 0.93 (3H, s). m/z (ES⁺, 70V) 418.1(MH⁺).

- 30 **EXAMPLE 2**

(2S)-2-[(4,4-Dimethyl-3-oxo-1-cyclobutenyl)amino]-3-[4-[(2,7)naphthyridin-1-yloxy]phenyl]propanoic acid

The compound of Example 1 (127mg, 0.31mmol) in THF (5ml) was treated in a single portion with LiOH.H₂O (13mg, 0.32mmol) in H₂O (1ml) and the

35 reaction stirred at room temperature for 2h. The reaction was then quenched by the addition of HOAc (glacial, 1ml) and the volatiles removed

in vacuo. Water (10ml) was then added to the residual foam and stirred vigorously to effect precipitation. The precipitate was then collected by vacuum filtration and the residue washed with water (2 x 5ml). Drying under vacuum gave the title compound as a fine white solid (108mg, 0.27mmol, 88%). δ H (DMSO d_6 , 300K) 9.67 (1H, s), 8.78 (1H, d, \downarrow 5.7Hz), 8.51 (1H, d, \downarrow 8.6Hz), 8.09 (1H, d, \downarrow 5.8Hz), 7.86 (1H, d, \downarrow 5.6Hz), 7.50 (1H, d, \downarrow 5.7Hz), 7.21 (2H, d, \downarrow 8.4Hz), 4.17 (2H, d, \downarrow 8.4Hz), 4.34 (1H, s), 4.18-4.14 (1H, m), 3.21 (1H, dd, \downarrow 4.9, 13.9Hz), 2.98 (1H, dd, \downarrow 13.9, 9.3Hz), 1.06 (3H, s), 0.99 (3H, s). m/z (ES⁺, 70V) 404.1 (MH⁺),

EXAMPLE 3

Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-[4-([2,6]naphthyridin-1-ylamino)phenyl]propanoate

A solution of 3-hydroxy-4,4-dimethyl-2-cyclobutenone (58mg, 0.51mmol) and Intermediate 2b3 (1.01g, 2.7mmol) in DCM (15ml), was stirred at room temperature for 48h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO₂; EtOAc) affording the title compound as a white powder (990mg, 2.3mmol, 88%). δ H (CDCl₃, 300K) 9.33 (1H, s), 9.24 (1H, s), 8.69 (1H, d, \downarrow 5.9Hz), 8.63 (1H, d, \downarrow 8.5Hz), 8.42 (1H, dd, \downarrow 5.9, 0.8Hz), 8.15 (1H, dd, \downarrow 5.7, 1.3Hz), 7.85-7.80 (3H, m), 7.31-7.22 (4H, m), 4.39 (1H, s), 4.24-4.21 (1H, m), 4.17 (2H, q, \downarrow 7.1Hz), 3.15 (1H, dd, \downarrow 13.8, 5.6Hz), 3.00 (1H, dd, \downarrow 13.8, 9.0Hz), 1.19 (3H, t, \downarrow 7.1Hz), 1.11 (3H, s), 1.05 (3H, s). m/z (ES⁺, 70V) 431.1 (MH⁺).

EXAMPLE 4

(2S)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-[4-([2,6]naphthyridin-1-ylamino)phenyl]propanoic acid

The compound of Example 3 (500mg, 1.16mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (421mg, 1.04mmol, 90%). δ H (DMSO d_6 , 300K) 9.21 (1H, s), 9.12 (1H, s br), 8.66 (1H, d, \downarrow 5.8Hz), 8.38 (1H, d, \downarrow 5.8Hz), 8.18 (2H, m), 7.81 (2H, d, \downarrow 7.9Hz), 7.27 (2H, d, \downarrow 7.9Hz), 7.26 (1H, obscured s), 4.36 (1H, s), 4.13-4.07 (1H, m), 3.20 (1H, dd, \downarrow 14.0, 5.1Hz) 3.02 (1H, dd, \downarrow 14.0, 8.7Hz), 1.13 (3H, s), 1.09 (3H, s). m/z (ES⁺, 70V) 403.0 (MH⁺).

EXAMPLE 5

Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

A solution of 3-hydroxy-4,4-dimethyl-2-cyclobutenone (58mg, 0.52mmol) [prepared according to the method of Wasserman, H.H. *et al* J. Org. Chem, 38, 1451-1455, (1973)] and Intermediate 27 (200mg, 5.2mmol), in DCM (5ml), was stirred at room temperature for 48h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO₂; EtOAc) affording the title compound as a white solid (230mg, 0.48mmol, 93%). δ H (CDCl₃, 300K) 8.48 (2H, s), 8.10 (1H, s), 7.51 (2H, d, \downarrow 8.2Hz), 7.04 (2H, d, 8.2Hz), 5.91 (1H, s), 4.43 (1H, s), 4.22 (2H, q, \downarrow 7.1Hz), 3.17 (1H, dd, \downarrow 14.0, 5.1Hz), 3.05 (1H, dd, \downarrow 14.0, 5.8Hz), 1.28 (3H, t, \downarrow 7.1Hz), 1.15 (3H, s), 1.14 (3H, s). m/z (ES⁺, 70V) 476.0 and 478.0 (MH⁺).

EXAMPLE 6

(2S)-2-[(4,4-dimethyl-3-oxo-1-cyclobutenyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid.

The compound of Example 5 (100mg, 0.21mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (76mg, 0.17mmol, 81%). δ H (DMSO d⁶, 350K) 10.5 (1H, s), 8.74 (2H, s), 7.80 (1H, broad s), 7.53 (2H, d, \downarrow 8.1Hz), 7.25 (2H, d, \downarrow 8.1Hz), 7.26 (1H, obscured s), 4.30 (1H, s), 3.88 (1H, m), 3.16 (1H, dd, \downarrow 13.5, 4.9Hz), 3.01 (1H, dd, \downarrow 13.5, 3.8Hz), 1.11 (3H, s), 1.07 (3H, s). m/z (ES⁺, 70V) 448.0 and 449.9 (MH⁺).

EXAMPLE 7

Methyl (2S)-2-[(4R,S)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

A solution of Intermediate 2 (187mg, 1.33mmol) and Intermediate 20 (450mg, 1.2mmol), in chloroform (10ml), was stirred at 55° for 48h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO₂; EtOAc) affording the title compound as a white solid (539mg, 1.17mmol, 91%) as an approx. 1:1 mixture of diastereomers. δ H (CDCl₃, 300K) 9.69 (1H, s), 8.69 (1H, d, \downarrow 5.7Hz), 7.51 (1H, dd, \downarrow 9.3, 0.5Hz), 7.19-7.11 (4H, m), 5.79 (1H, d, \downarrow 7.3Hz), 4.64 (1H, s), 4.36-4.30 (1H, m), 3.84 and 3.82 (3H, s, diastereomeric CH₃), 3.31-3.15 (2H, m), 2.45 (3H, s), 1.59-

1.54 (1H, m), 1.50-1.4 (1H, m), 1.34-1.23 (2H, m), 1.28 and 1.27 (3H, s, diastereomeric CH₃), 0.91-0.86 (3H, m). m/z (ES⁺, 70V) 460.1 (MH⁺).

EXAMPLE 8

5 **(2S)-2-[(4R,S)-4-Methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl]propanoic acid**

The compound of Example 7 (230mg, 0.5mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (198mg, 0.44mmol, 79%) as an approx. 1:1 mixture of diastereomers. δ H (DMSO d₆, 300K) 13.0 (1H, s), 9.60 (1H, d, \downarrow 9.7Hz), 8.72 (1H, d, \downarrow 5.6Hz), 8.49-8.43 (1H, m NH), 7.76 (1H, d, \downarrow 4.7Hz), 7.41-7.34 (2H, m), 7.27-7.21 (2H, m), 4.47 and 4.43 (1H, s), 4.19-4.13 (1H, m), 3.29-3.23 (3H, s, and 1H as obscured m), 3.02-2.97 (1H, m), 2.36 and 2.35 (3H, s), 1.50-1.10 (4H, m), 1.08 and 0.98 (3H, s), 0.84-0.63 (3H, m),
15 m/z (ES⁺, 70V) 446.1 and 447.1 (MH⁺).

EXAMPLE 9

Ethyl (2S)-2-[(4,4-dipropyl-3-oxo-1-cyclobutenyl)amino]-3-[4-[(2,7]naphthyridin-1-yl)oxy]phenyl]propanoate

20 A solution of Intermediate 4 (180mg, 1.07mmol) and the ethyl ester of Intermediate 13 (362mg, 1.07mmol), in chloroform (7ml), was stirred at room temperature for 96h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO₂; EtOAc) affording the title compound as a white solid (406mg, 0.83mmol, 78%). δ H (CDCl₃, 300K) 9.72 (1H, s), 8.71 (1H, d \downarrow 5.7Hz), 8.04 (1H, d, \downarrow 5.8Hz), 7.55 (1H, d, \downarrow 5.7Hz), 7.22-7.16 (4H, m), 5.67 (1H, d, \downarrow 7.9Hz), 4.64 (1H, s), 4.26-4.16 (3H, m), 3.20 (1H, dd, \downarrow 14.1, 5.7Hz), 3.11 (1H, dd, \downarrow 14.1, 6.6Hz), 1.58-1.01 (8H, m), 0.81 (6H, t, \downarrow 7.0Hz). m/z (ES⁺, 70V) 488.1 and 489.1 (MH⁺).

30 **EXAMPLE 10**

(2S)-2-[(3-Oxo-4,4-dipropyl-1-cyclobutenyl)amino]-3-[4-[(2,7]naphthyridin-1-yl)oxy]phenyl]propanoic acid

The compound of Example 9 was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine off-white powder
35 (35mg, 0.07mmol, 19%). δ H (DMSO d₆, 350K) 9.68 (1H, s), 8.83 (1H, d, \downarrow 5.7Hz), 8.37 (1H, d, \downarrow 8.5Hz), 8.14 (1H, d, \downarrow 5.8Hz), 7.91 (1H, d, \downarrow 5.7Hz),

7.55 (1H, d, \downarrow 5.8Hz), 7.39 (2H, d, \downarrow 8.4Hz), 7.28 (2H, d, \downarrow 8.4Hz), 4.53 (1H, s), 4.14 (1H, dd, \downarrow 9.8, 4.3Hz), 3.25 (1H, dd, \downarrow 14.0, 4.6Hz), 3.0 (1H, dd, \downarrow 10.3, 14.0Hz), 1.50-0.64 (14H, m). m/z (ES⁺, 70V) 460.1 and 461.1 (MH⁺).

5

EXAMPLE 11**Ethyl (2R)-2-[(4R,S)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-[(2,7)naphthyridin-1-yloxy]phenyl]propanoate**

A solution of Intermediate 2 (300mg, 2.1mmol) and the ethyl ester of
 10 Intermediate 13 (724mg, 2.14mmol), in DCM (15ml), was stirred at room temperature for 24h. The reaction was then diluted with DCM (30ml) and distilled water (20ml) and washed successively with 1M aqueous hydrochloric acid (30ml) water (30ml) and saturated, aqueous sodium hydrogen carbonate (30ml). The organic layer was then dried (MgSO₄),
 15 filtered and concentrated *in vacuo*. The residual foam was chromatographed (SiO₂; EtOAc) affording the title compound as a white powder (827mg, 1.8mmol, 84%) as an approx. 1:1 mixture of diastereomers. δ H (CDCl₃, 300K) 9.72 (1H, s), 8.71 (1H, d, \downarrow 5.7Hz), 8.04 (1H, d, \downarrow 5.8Hz), 7.55 (1H, d, \downarrow 5.7Hz), 7.22-7.12 (5H, m), 5.80 (1H, d, \downarrow 7.6Hz), 4.57 (1H, s), 4.28-4.20 (3H, m), 3.25-3.07 (2H, m), 1.57-1.21
 20 (7H, m), 1.18 and 1.17 (3H, s) 0.84-0.78 (3H, m). m/z (ES⁺, 70V) 460.1 (MH⁺) and 482.0 (MNa⁺).

EXAMPLE 12**(2R)-2-[(4R,S)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-[(2,7)naphthyridin-1-yloxy]phenyl]propanoic acid**

The compound of Example 11 (600mg, 1.31mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (520mg, 1.21mmol, 92%) as an approx. 1:1 mixture of
 30 diastereomers. δ H (DMSO d₆, 300K) 9.61 and 9.58 (1H, s), 8.72 (1H, d, \downarrow 5.7Hz), 8.39-8.33 (1H, m NH), 8.04-8.00 (1H, m), 7.80-7.79 (1H, m), 7.45-7.33 (1H, m), 7.32-7.25 (2H, m), 7.18-7.12 (2H, m), 4.37 and 4.32 (1H, s), 4.10-4.04 (1H, m), 3.17-3.12 (1H, m), 2.94-2.82 (1H, m), 1.41-0.86 (4H, m), 0.99 and 0.91 (3H, s) 0.73 and 0.63 (3H, t, \downarrow 7.2Hz). m/z (ES⁺,
 35 70V) 432.0 (MH⁺).

EXAMPLE 13**Ethyl (2S)-2-[(4R,S)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-[(2,6)naphthyridin-1-ylamino]phenyl]propanoate**

Prepared from Intermediate 2 (200mg, 1.43mmol) and Intermediate 23 (400mg, 1.19mmol), in a similar manner to the compound of Example 11 to give the title compound as an approx. 1:1 mixture of diastereomers as a white powder (482mg, 1.05mmol, 89%). δ H (CDCl₃, 300K) 9.13 (1H, s), 8.61 (1H, d, \downarrow 5.9Hz), 8.17 (1H, d, \downarrow 5.8Hz), 7.66-7.60 (3H, m), 7.19-7.04 (5H, m), 5.62 (1H, t, \downarrow 4.6Hz), 4.51 and 4.49 (1H, s), 4.25-4.19 (3H, m), 3.16-3.05 (2H, m), 1.51-1.16 (7H, m), 0.85-0.77 (3H, m). m/z (ES⁺, 70V) 459.1 (MH⁺).

EXAMPLE 14**(2S)-2-[(4R,S)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-[(2,6)naphthyridin-1-ylamino]phenyl]propanoic acid**

The compound of Example 13 (600mg, 1.31mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a pale yellow powder (521mg, 1.21mmol, 95%) (approx. 1:1 mixture of diastereomers). δ H (DMSO d₆, 300K) 9.10 (1H, s), 8.55-8.53 (1H, m), 8.37 and 8.31 (1H, m NH), 8.27 (1H, d, \downarrow 5.9Hz), 7.72-7.65 (2H, m), 7.15-7.08 (3H, m), 4.30 and 4.25 (1H, s), 3.99-3.94 (1H, m), 3.06-2.99 (1H, m), 2.83-2.76 (1H, m), 1.34-0.96 (4H, m), 0.94 and 0.86 (3H, s), 0.68 and 0.55 (3H, t, \downarrow 7.0Hz). m/z (ES⁺, 70V) 431.0 (MH⁺).

EXAMPLE 15**Ethyl (2S)-2-[(4R,S)-4-methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate**

Prepared from Intermediate 2 (120mg, 0.86mmol) and Intermediate 27 (300mg, 0.79mmol), in a similar manner to the compound of Example 11 to give title compound as an approx. 1:1 mixture of diastereomers as a white powder (318mg, 0.63mmol, 80%). δ H (CDCl₃, 300K) 8.56 (2H, s), 8.29 and 8.24 (1H, s NH), 7.61-7.59 (2H, m), 7.16-7.10 (2H, m), 5.82 -5.78 (1H, m), 4.56 (1H, s), 4.32-4.26 (3H, m), 3.29-3.23 (1H, m), 3.16-3.09 (1H, m), 1.59-1.13 (7H, m), 0.89-0.84 (3H, m). m/z (ES⁺, 70V) 504.0 and 506.0 (MH⁺).

EXAMPLE 16**(2S)-2-[(4R,S)-4-Methyl-3-oxo-4-propyl-1-cyclobutenyl]amino-3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]propanoic acid**

The compound of Example 15 (300mg, 0.59mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (261mg, 0.55mmol, 92%) (approx. 1:1 mixture of diastereomers). δ H (DMSO d_6 , 300K) 10.90 (1H, s), 8.81 (2H, s), 7.60-7.56 (2H, m), 7.31-7.26 (2H, m), 4.45 and 4.42 (1H, s), 4.15-4.41 (1H, m), 3.23-3.14 (1H, m), 2.99-2.89 (1H, m), 1.49-1.12 (3H, m), 1.07 and 0.99 (3H, s), 0.84-0.54 (4H, m). m/z (ES⁺, 70V) 476.0 and 478.0 (MH⁺).

EXAMPLE 17**Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate**

Prepared from Intermediate 6 (200mg, 1.0mmol) and Intermediate 27 (200mg, 0.52mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (201mg, 0.42mmol, 72%). δ H (CDCl₃, 300K) 8.99 (1H, s), 8.42 (2H, s), 7.52 (2H, d, J 8.4Hz), 7.02 (2H, d, J 7.6Hz), 5.54 (1H, s), 4.34 (1H, s), 4.19 (2H, q, J 7.1Hz), 3.07 (2H, br s), 1.95-1.81 (2H, br s), 1.27-0.77 (17H, m). m/z (ES⁺, 70V) 560.0 and 562.0 (MH⁺).

EXAMPLE 18**(2S)-2-[(4,4-Dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoic acid**

The compound of Example 17 (80mg, 0.14mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as an off-white powder (62mg, 0.12mmol, 82%). δ H (DMSO d_6 , 300K) 10.53 (1H, s), 8.73 (2H, s), 7.60-7.56 (2H, m), 7.57 (2H, d, J 8.4Hz), 7.30 (2H, d, J 8.4Hz), 4.14-4.12 (1H, m), 3.17 (1H, dd, J 13.9, 4.8Hz), 3.03 (1H, dd, J 13.0, 9.1Hz), 1.87 (2H, t, J 7.3Hz), 1.41-1.25 (9H, m), 1.15-0.86 (8H, m). m/z (ES⁺, 70V) 532.0 and 534.0 (MH⁺).

EXAMPLE 19**Ethyl (2S)-2-[(4,4-dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-[4-[(2,7)naphthyridin-1-yloxy]phenyl] propanoate**

Prepared from Intermediate 6 (200mg, 1.0mmol) and the ethyl ester of Intermediate 13 (200mg, 0.59mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (201mg, 0.42mmol, 72%). δ H (CDCl₃, 300K) 9.72 (1H, s), 8.71 (1H, d, \downarrow 5.7Hz), 8.03 (1H, d, \downarrow 5.8Hz), 7.56-7.51 (1H, m), 7.27-7.17 (4H, m), 5.41 (1H, br m), 4.39 (1H, br m), 4.19 (2H, q, \downarrow 7.1Hz), 3.15-3.12 (2H, m), 1.91-1.75 (2H, m), 1.39-1.09 (18H, m), 0.81-0.74 (2H, m). m/z (ES⁺, 70V) 516.1 (MH⁺).

10 **EXAMPLE 20**

(2S)-2-[(4.4-Dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-[4-[(2.7)naphthyridin-1-yloxy]phenyl]propanoic acid

The compound of Example 19 (200mg, 0.39mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (161mg, 0.33mmol, 85%). δ H (DMSO d₆, 360K) 9.62 (1H, s), 8.74 (1H, d, \downarrow 5.6Hz), 8.04 (1H, d, \downarrow 5.6Hz), 7.82 (1H, d, \downarrow 5.6Hz), 7.47 (1H, d, \downarrow 5.5Hz), 7.30 (2H, d, \downarrow 8.3Hz), 7.17 (2H, d, \downarrow 8.3Hz), 4.02 (1H, br s), 3.21-3.18 (1H, m), 2.97-2.91 (1H, m), 1.74 (2H, m), 1.12-0.62 (17H, m). m/z (ES⁺, 70V) 488.1 (MH⁺).

20

EXAMPLE 21

Ethyl (2S)-2-[(4.4-dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-[4-[(3-methyl[2.7)naphthyridin-1-yl]oxy]phenyl]propanoate

Prepared from Intermediate 6 (200mg, 1.0mmol) and Intermediate 18 (300mg, 0.85mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (331mg, 0.63mmol, 73%). δ H (CDCl₃, 300K) 9.70 (1H, s), 8.70 (1H, d, \downarrow 5.8Hz), 7.51 (1H, d, \downarrow 5.8Hz), 7.26-7.19 (4H, m), 5.34 (1H, br s), 4.45 (1H, br s), 4.26 (2H, q, \downarrow 7.2Hz), 3.21 (2H, br s), 2.44 (3H, s), 2.10-1.90 (2H, m), 1.47-1.43 (2H, m), 1.33-1.12 (12H, m), 0.87-0.84 (3H, m). m/z (ES⁺, 70V) 530.1 (MH⁺).

EXAMPLE 22

(2S)-2-[(4.4-dimethyl-3-oxo-2-hexyl-1-cyclobutenyl)amino]-3-[4-[(3-methyl[2.7)naphthyridin-1-yl]oxy]phenyl]propanoic acid

35 The compound of Example 21 (60mg, 0.11mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as

a fine white solid (42mg, 0.08mmol, 74%). δ H (DMSO d_6 , 360K) 9.59 (1H, s), 8.70 (1H, d, \downarrow 5.7Hz), 7.70-7.68 (1H, m), 7.66 (1H, d, \downarrow 9.7Hz), 7.37 (2H, d, \downarrow 8.6Hz), 7.31 (1H, s), 7.23 (2H, d, \downarrow 8.6Hz), 4.18-4.16 (1H, m), 3.24 (1H, dd, \downarrow 13.9, 4.4Hz), 3.04 (1H, dd, \downarrow 13.9, 9.9Hz), 2.38 (3H, s), 1.86 (2H, t, \downarrow 7.3Hz), 1.38-1.19 (8H, m), 1.04 (3H, s), 0.99 (3H, s), 0.83-0.79 (3H, m). m/z (ES⁺, 70V) 502.1 (MH⁺).

EXAMPLE 23

Ethyl (2S)-2-[(4R,S)-4-benzyl-4-methyl-3-oxo-1-cyclobutenyl]amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoate

Prepared from Intermediate 8 (200mg, 1.0mmol) and Intermediate 20 (300mg, 0.85mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (412mg, 0.79mmol, 92%) as an approx. 1:1 mixture of diastereomers. δ H (CDCl₃, 300K) 9.70 (1H, d, \downarrow 4.9Hz), 8.71 and 8.70 (1H, d, \downarrow 5.8Hz), 7.51 (1H, d, \downarrow 5.8Hz), 7.31-7.08 (11H, m), 5.88-5.82 (1H, m), 4.60 and 4.50 (1H, s), 4.33-4.28 (1H, m), 4.26-4.16 (2H, m), 3.25-3.07 (2H, m), 2.98-2.83 (2H, m), 2.45 and 2.40 (3H, s), 1.35-1.21 (6H, m). m/z (ES⁺, 70V) 522.1 (MH⁺).

EXAMPLE 24

(2S)-2-[(4R,S)-4-Benzyl-4-methyl-3-oxo-1-cyclobutenyl]amino-3-{4-[(3-methyl[2,7]naphthyridin-1-yl)oxy]phenyl}propanoic acid

The compound of Example 23 (250mg, 0.48mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (221mg, 0.45mmol, 94%) as an approx. 1:1 mixture of diastereomers. δ H (DMSO d_6 , 360K) 9.72 (1H, m), 8.81 (1H, m), 8.03 (1H, m), 7.82-7.77 (1H, br m), 7.46-7.20 (9H, m), 4.49 and 4.41 (1H, s), 4.21 (1H, m), 3.39-3.30 (1H, m), 3.21-3.14 (1H, m), 3.01-2.87 (2H, m), 2.51 (3H, s), 1.29 and 1.24 (3H, s). m/z (ES⁺, 70V) 494.0 (MH⁺).

EXAMPLE 25

Ethyl (2S)-2-[(4R,S)-4-benzyl-4-methyl-3-oxo-1-cyclobutenyl]amino-3-4-{(3,5-dichloroisonicotinoyl)amino}phenylpropanoate.

Prepared from Intermediate 8 (185mg, 0.98mmol) and the free amine of Intermediate 27 (300mg, 0.79mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (387mg,

0.70mmol, 89%) as an approx. 1:1 mixture of diastereomers. δ H (CDCl₃, 300K) 9.36 and 9.31 (1H, s), 8.36 and 8.35 (2H, s), 7.54 and 7.45 (1H, d, \downarrow 8.4Hz), 7.19-7.02 (8H, m), 6.09-6.03 (1H, m), 4.31 and 4.20 (1H, s), 4.22-4.01 (3H, m), 3.07-2.92 (2H, m), 2.76-2.63 (2H, m), 1.35-1.15 (2H, m), 1.09 and 1.08 (3H, s). m/z (ES⁺, 70V) 551.9 and 553.9 (MH⁺).

EXAMPLE 26

(2S)-2-[(4R,S)-4-Benzyl-4-methyl-3-oxo-1-cyclobutenyl]amino-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 25 (320mg, 0.58mmol) was hydrolysed in a similar manner to the method of Example 12 to give the title compound as a fine white solid (277mg, 0.53mmol, 91%) as an approx. 1:1 mixture of diastereomers. δ H (DMSO d₆, 360K) 13.05 (1H, br s), 8.83 and 8.82 (2H, s), 8.67 and 8.62 (1H, d, \downarrow 8.9Hz), 7.71 and 7.61 (2H, d, \downarrow 8.7Hz), 7.37-6.89 (9H, m), 4.32 and 4.23 (1H, s), 4.09-4.00 (1H, m), 3.20-2.64 (4H, m), 1.24-1.07 (3H, m). m/z (ES⁺, 70V) 523.9 and 525.9 (MH⁺).

EXAMPLE 27

Ethyl (2S)-2-[(3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoate

Prepared from 1-keto-3-hydroxyspiro[3,5]-non-2-ene (400mg, 2.6mmol) [prepared according to the method of Wasserman, H.H. *et al*, J. Org. Chem., **38**, 1451-1455 (1973)] and the free amine of Intermediate 27 (400mg, 1.04mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (512mg, 0.99mmol, 95%). δ H (CDCl₃, 300K) 10.86 (1H, s), 8.78 (2H, s), 8.34 (1H, d, \downarrow 8.5Hz), 7.56 (2H, d, \downarrow 8.5Hz), 7.25 (2H, d, \downarrow 8.5Hz), 4.36 (1H, s), 4.20-4.11 (3H, m), 3.13 (1H, dd, \downarrow 13.8, 5.3Hz), 3.00 (1H, dd, \downarrow 9.2, 13.8Hz), 1.67-1.19 (10H, m), 1.17 (3H, t, \downarrow 4.1Hz). m/z (ES⁺, 70V) 516.0 and 518.0 (MH⁺).

EXAMPLE 28

(2S)-2-[(3-Oxospiro[3.5]non-1-en-1-yl)amino]3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid

The compound of Example 27 (700mg, 1.36mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (627mg, 1.28mmol, 95%). δ H (DMSO d₆, 360K) 10.54

(1H, s), 8.73 (2H, s), 7.81 (1H, d, \downarrow 8.4Hz), 7.56 (2H, d, \downarrow 8.5Hz), 7.27 (2H, d, \downarrow 8.5Hz), 4.39 (1H, s), 4.12-4.05 (1H, m), 3.19 (1H, dd, \downarrow 13.9, 5.1Hz), 3.00 (1H, dd, \downarrow 13.9, 8.8Hz), 1.94-1.24 (10H, m). m/z (ES⁺, 70V) 488.0 and 490.0 (MH⁺).

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EXAMPLE 29

Ethyl (2S)-2-[(3-oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3-methyl[2.7]naphthyridin-1-yl)oxy]phenyl}propanoate

Prepared from 1-keto-3-hydroxyspiro[3,5]-non-2-ene (400mg, 2.6mmol) and Intermediate 20 (400mg, 1.14mmol), in a similar manner to the compound of Example 11 to give the title compound as a white powder (497mg, 1.02mmol, 89%). δ H (CDCl₃, 300K) 9.62 (1H, s), 8.72 (1H, d, \downarrow 5.7Hz), 7.99 (1H, d, \downarrow 8.6Hz), 7.73 (1H, dd, \downarrow 5.7, 0.9Hz), 7.37-7.34 (3H, m), 7.28-7.24 (2H, m), 4.42 (1H, s), 4.26-4.18 (3H, m), 3.25 (1H, dd, \downarrow 14.0, 5.6Hz), 3.12 (1H, dd, \downarrow 14.0, 9.1Hz), 2.42 (3H, s), 1.72-1.55 (10H, m), 1.25 (3H, t, \downarrow 7.1Hz). m/z (ES⁺, 70V) 486.1 (MH⁺).

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EXAMPLE 30

(2S)-2-[(3-Oxospiro[3.5]non-1-en-1-yl)amino]-3-{4-[(3-methyl[2.7]naphthyridin-1-yl)oxy]phenyl}propanoic acid

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The compound of Example 29 (300mg, 0.62mmol) was hydrolysed in a similar manner to the method of Example 2 to give the title compound as a fine white solid (237mg, 0.52mmol, 84%). δ H (DMSO d₆, 360K) 9.62 (1H, s), 8.72 (1H, d, \downarrow 5.7Hz), 7.82 (1H, d, \downarrow 6.3Hz), 7.73 (1H, d, \downarrow 5.5Hz), 7.35 (2H, d, \downarrow 8.7Hz), 7.25 (2H, d, \downarrow 8.7Hz), 4.39 (1H, s), 4.12 (1H, dd, \downarrow 8.7, 13.2Hz), 3.34-3.12 (2H, m), 2.42 (3H, s), 1.72-1.53 (10H, m). m/z (ES⁺, 70V) 458.0 (MH⁺).

25

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

35

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with F(ab)₂ fragment goat anti-human IgG Fc γ -specific antibody [Jackson Immuno Research 109-006-098: 100 μ l at 2 μ g/ml in 0.1M NaHCO₃, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 μ l containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100 μ l methanol for 10 minutes followed by another wash. 100 μ l 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100 μ l 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β -lympho blastoid cell-line JY was used in place of Jurkat cells. The IC₅₀ value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5 μ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100 μ l PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200 μ l containing 2.5×10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated

test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic

- 5 96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2×10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200 μ l in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence
10 or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100 μ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min.
15 Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50 μ g/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

20 **$\alpha_{IIb}\beta_3$ -dependent human platelet aggregation**

- Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and
25 diluted to a cell density of 6×10^8 /ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $MgCl_2 \cdot H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0; $NaHPO_4 \cdot 2H_2O$ 0.065). Aggregation was monitored following addition of 2.5 μ M ADP (Sigma) in the presence or absence of inhibitors.

- 30 In the above assays the preferred compounds of the invention such as the compounds of the Examples generally have IC_{50} values in the $\alpha_4\beta_1$ and assay of 1 μ M and below and in the $\alpha_4\beta_7$ assay of 5 μ M and below. In the other assays featuring α integrins of other subgroups the same
35 compounds had IC_{50} values of 50 μ M and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

